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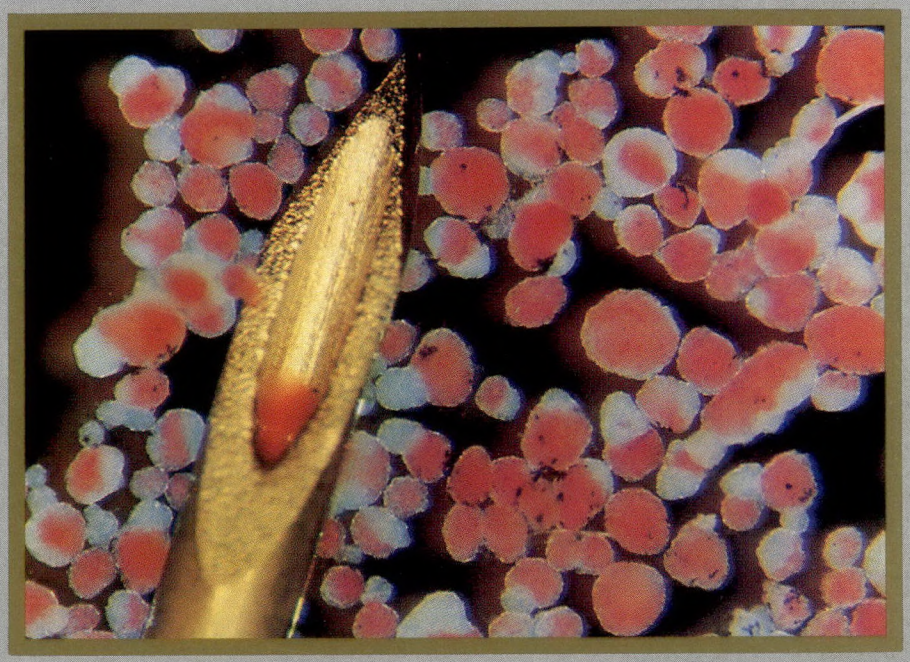

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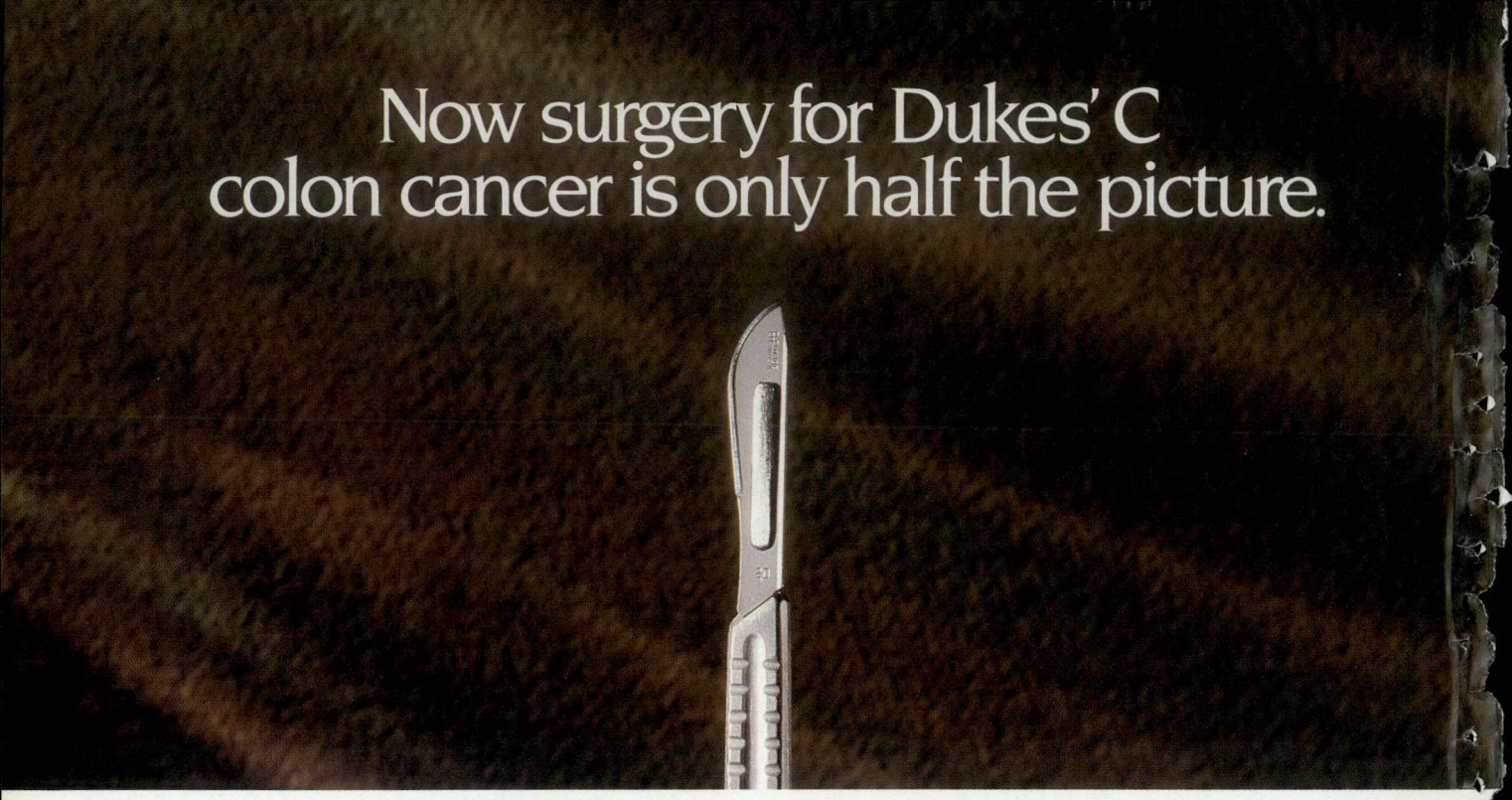
Now surgery for Dukes' C colon cancer is only half the picture.



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LEVAMISOLE AND FLUOROURACIL FOR ADJUVANT THERAPY OF RESECTED COLON CARCINOMA

Abstract Twelve hundred ninety-six patients with resected colon cancer that either was locally invasive (Stage B_2) or had regional nodal involvement (Stage C) were randomly assigned to observation or to treatment for one year with levamisole combined with fluorouracil. Patients with Stage C disease could also be randomly assigned to treatment with levamisole alone. The median follow-up time at this writing is 3 years (range, 2 to 5½).

Among the patients with Stage C disease, therapy with levamisole plus fluorouracil reduced the risk of cancer recurrence by 41 percent ($P < 0.0001$). The overall death rate was reduced by 33 percent ($P \approx 0.006$). Treatment with levamisole alone had no detectable effect. The results in the patients with Stage B_2 disease were equivocal and too preliminary to allow firm conclusions. Toxic effects of levamisole alone were infrequent, usually consisting of mild nausea with occasional dermatitis or leukopenia, and those of levamisole plus fluorouracil were essentially the same as those of fluorouracil alone—i.e., nausea, vomiting, stomatitis, diarrhea, dermatitis, and leukopenia. These reactions were usually not severe and did not greatly impede patients' compliance with their regimen.

We conclude that adjuvant therapy with levamisole and fluorouracil should be standard treatment for Stage C colon carcinoma. Since most patients in our study were treated by community oncologists, this approach should be readily adaptable to conventional medical practice. (N Engl J Med 1990; 322:352-8.)[1]

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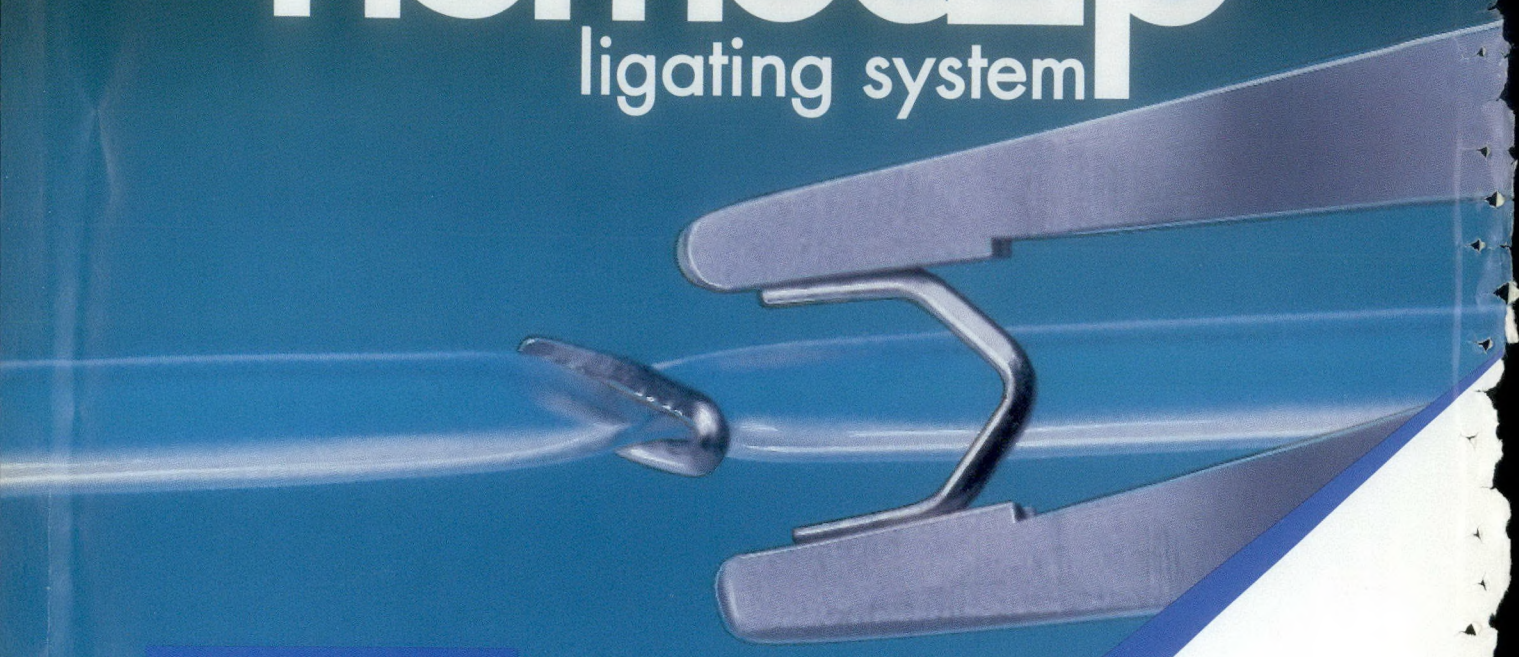

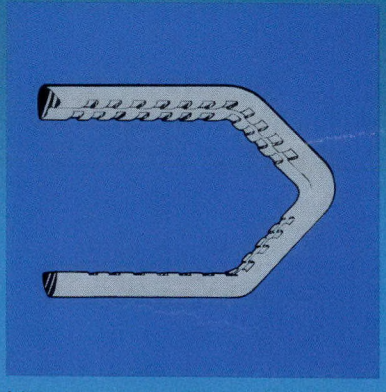

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Early Gastric Cancer — Making the Asymptomatic Better

N. Schmidt, MD, FRCSC

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Gastric cancer doesn't seem to raise the same interest among surgeons it once did. This isn't because the subject is uninteresting or inconsequential but because there is a sense of futility in treating a devastating disease with a uniformly poor outcome, unless the surgeon is fortunate enough to diagnose early gastric cancer (EGC).

Is EGC a distinct entity or is it merely the beginning of a spectrum of gastric mucosal neoplasia? Hampson and colleagues from McGill University and the Montreal General Hospital address that question in this issue (pages 349 to 352). Of their 199 cases of gastric carcinoma gathered between 1970 and 1981, 26 by their definition (confined to mucosa or submucosa) were EGC. The authors correlate well the outcome of gastric cancer with depth of tumour penetration into the stomach wall; however, they do not totally address the question of whether EGC is a distinct entity, even though they believe it is merely part of a continuum of an advancing disease.

Because it may occur repetitively in family groups, may be indolent and may even recur in an early superficial and local manner, it is still argued by some[1] that EGC is a distinct gastric entity with a more favourable biologic nature than other forms of gastric cancer. Most workers — and here one must pay strict attention to the Japanese studies — consider EGC to be an early stage of progressive and aggressive gastrointestinal malignant disease. As a result enormous efforts have been made in Japan toward screening for the early diagnosis of gastric carcinoma, which is the most common malignant disease in that country.

Early gastric cancer is indeed associated with a favourable statisti-

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Detailed instructions to contributors, in English and French, appear on pages 77 and 78 of the February 1990 issue.

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cal survival rate. Takagi and Nakada[2] studied 383 cases of EGC. Their 5-year survival was 94% in patients who had no lymph-node involvement, 74% in patients who had regional lymph-node involvement, 64% in those who had secondary lymph-node involvement and 26% in those who had remote metastases. Other large series[3] from Japan have supported the optimistic figures of Takagi and Nakada. But the detection of EGC requires a screening program of immense complexity and cost. Nationwide screening for gastric carcinoma carried out in 1985 in Japan alone involved 5 161 876 patients, and a positive diagnosis was made in only 6240 patients (0.12%).

There is no doubt that screening for malignant disease has reduced the clinical severity of carcinoma of the cervix, breast and colon. Screening does not change the prevalence of a disease; it merely aims at early detection. However, if the incidence of a disease is decreasing, the benefits of a costly screening program are hard to document, since the reduced morbidity and mortality may not be the end result of early detection through screening but of a decreasing prevalence of the disease. Since the incidence of EGC is not rising in relation to advanced gastric carcinoma, EGC is most likely an early form of a disease with various biologic presentations and behaviour.[4]

How can gastric cancer be attacked at a more treatable stage? With such optimistic results from the treatment of EGC and such dismal ones from advanced gastric cancer, the answer can only come through screening programs for EGC. Unfortunately to organize a program such as this in Canada is a near impossibility. Mass screening through upper gastrointestinal roentgenography and endoscopy with biopsy at a time when a patient is asymptomatic is almost impossible. The cost, inconvenience, small risk, lack of personnel and facilities, and failure of patient compliance has prevented even mass screening for colonic cancer with simple Hemoccult testing, which bears no comparison with the complexity of an EGC screening program. In 1985 in Canada gastric carcinoma was diagnosed in 1833 men and 1077 women. If 1% of the patients had true EGC, only 28 patients could expect the favourable results of the Japanese experience, if patients had no nodal involvement and if gastric cancer in Japan and Canada has similar biologic behaviour. The Japanese detection rate of EGC of 0.12% makes the likelihood of diagnosis in a Canadian screening program even less. It is expected that in 1990 a similar number of cases of gastric carcinoma with be diagnosed, this number being only 3% to 4% of all diagnosed malignant disease, 14.3% of lung cancer in men and 16.7% of breast cancer in women. A national screening program for detecting EGC with these statistics would hardly be cost effective and is unlikely to be health effective.[5]

What then do we do with gastric carcinoma? Massive screening projects are out of the question. Most people suffer epigastric symptoms 6 to 9 months before gastric carcinoma is diagnosed and are sent for investigation of epigastric symptoms only after a period of initial therapy has failed. By being aware of the possibility of EGC and knowing the favourable results from treating it, primary physicians must send their patients for more thorough assessment before the disease has a chance to become advanced. Premalignant conditions can be identified and EGC could fortuitously be found, and the asymptomatic patient could indeed be made to feel better.

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Reproductive Conservation

John F. Jarrell, MD, FRCSC

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One of the most powerful human needs is the need to reproduce. Although this is sometimes poorly understood, all cultures share in the celebration of birth and the renewal of the life cycle. In medicine, disorders of fertility are considered physical handicaps of the reproductive system and, although not life threatening, they take their toll on the individual's quality of life, particularly in cases of permanent sterility.

During the past decade new procedures have evolved, which are collectively known as the "assisted reproductive technologies". These procedures are primarily indicated for established infertility, which may be due to disorders of semen, fallopian tubes or ovulation or to other abnormalities. They include almost all possible forms of interaction of the human gametes alone or in combination. What is not generally appreciated is the extent to which these procedures may be used to prevent the loss of reproductive capacity when it is vulnerable to the effects of treatment for serious medical conditions such as cancer. In this editorial I describe briefly those assisted reproductive technologies that may benefit patients likely to become sterile as a result of cancer treatment.

What are these procedures and how do they affect the gynecologist's clinical practice? For young men facing certain sterility, usually as a result of treatment for testicular cancers or various lymphomas, there are two main types of support, depending on the time frame. Men who have been sterilized usually present to fertility clinics with a request for donor insemination. This technique has been substantially modified in the past decade because of the risk of transmitting the human immunodeficiency virus through semen and blood products and the resultant need for quarantine of the semen. In general recipients find this a satisfactory procedure although, in addition to the small risk of acquired immunodeficiency syndrome, there remains an unfortunate uncertainty and legal vacuum with respect to the legislation of parenthood.

The other possibility for young men may be considered at the time of diagnosis when there is a brief window of opportunity in which semen may be cryopreserved for use later when the need for progeny may be more appropriate. For this to be successful, those managing the condition that will render the man sterile should at least discuss the subject of semen cryopreservation with the patient. Although some patients may be unable to produce a sample of semen, they appreciate the opportunity. There are concerns about the efficiency of this service in achieving the desired outcome, but it is reassuring that techniques enabling the insemination of a single spermatozoon into an oocyte are currently being developed in animal models using in-vitro techniques. These techniques may also help to offset the deleterious effects of serious diseases, particularly the lymphomas, on spermatogenesis.

With respect to young women, the therapy parallel to semen donation is oocyte donation. This may be done following treatment that has produced gonadal failure. It is possible to maintain pregnancy among such women by appropriate administration of estrogen and progesterone. The oocyte is commonly donated by either a friend or a relative or from an anonymous source, usually a patient at an in-vitro fertilization clinic. The treatment can be quite successful, and for many the limiting factor is an acceptable source of oocytes. It is fortunate that access to the ovarian follicles has recently been facilitated by the ultrasonographic vaginal approach to follicle aspiration. This reduces the risk to the donor.

At present there is no technique to parallel the cryopreservation of semen. Cryopreservation is generally considered to place the oocyte at risk because of the large size of the cell and the vulnerability of chromatin during the final stages of meiosis when the follicles are aspirated. Alternatively, young women suffering from a condition that will render them sterile can undergo a course of ovarian stimulation and oocyte recovery after which the oocytes may be fertilized by semen from the patient's partner and the resultant embryos cryopreserved indefinitely. There is a concern that the time required for the stimulation cycle and oocyte recovery may extend from 2 to 4 weeks and thereby cause additional risk from the original medical condition. This may be alleviated in the

future as a result of recent reports that an oocyte may be induced to undergo maturation in vitro. Further, the availability of ovarian perfusion techniques may decrease these concerns.

The new techniques are an important contribution to the holistic approach to the patient with cancer. They are becoming popular because of the failure of other methods, such as ovarian repositioning before irradiation, and the uncertainty of the effectiveness of luteinizing hormone releasing-hormone analogues in suppressing and maintaining gonadal function during chemotherapy. For these new techniques to be effective, however, there must be improved communication between reproductive endocrine and oncology services, improved patient awareness of fertility and its relation to cancer and further study of the important changes in human relationships that may occur as a result of these treatments.

The recently announced royal commission directed to evaluate the new reproductive techniques in Canada will provide an opportunity to increase awareness of such therapies and their implications.■

BOOK REVIEWS

THORACIC SURGERY. Edited by H. Pichlmaier and F.W. Schildberg. 460 pp. Illust. Springer-Verlag New York, Inc., Secaucus, NJ, 1989. $375.00 (US). ISBN 0-387-18464-3

This well-referenced book provides a descriptive account of general thoracic surgery. All of the chapters have subheadings, which makes it easy to find specific topics. The thrust of the book is toward the indications for specific general thoracic surgical procedures as well as detailed, practical aspects of the operative procedures themselves. Not enough emphasis is given to the pathophysiology of disease processes.

The first chapters outline functional studies for assessing operability and describe the peri- and postoperative care of thoracic surgical patients. A discussion of comparative outcomes of operative procedures in various disease states would have added stature to this book.

The chapter on trauma to the thoracic wall and chest-wall disease is short on the pathophysiologic aspects of chest-wall injury, but operative procedures and reconstruction of the thoracic cage are elegantly described with the aid of excellent diagrams. However, the book neglects to mention nonoperative management of thoracic wall trauma, and little mention is made of the developing use of myocutaneous flaps in chest-wall reconstruction. In terms of thoracic trauma, not enough emphasis is given to the emergency management of life-threatening thoracic trauma involving the lung parenchyma.

The section on the lung and tracheobronchial tree is especially strong in defining the indications for surgery in a wide variety of pathologic conditions affecting the lung. Methods of surgical lung resection are precisely described in a step-by-step fashion, together with possible complications and ways to avoid them. Statements about outcomes, again, are lacking.

The authors present a well-illustrated, detailed description and debate of the indications and relative merits of different approaches to surgical resection and reconstruction of the esophagus for various disease states and operative conditions. They, quite rightly, favour the use of stomach over jejunum and colon as an esophageal substitute. In situations in which the stomach cannot be used as a substitute, they favour the use of colon over jejunum and limit the use of jejunum to replace the lower esophagus. The jejunum, however, can be used to replace the whole esophagus and can, in most patients, be elevated to the level of the neck. Although preparation of a jejunal segment for transposition to the neck is difficult and requires meticulous technique, its function is superior to that of colon. The technique requires dissecting free the peritoneum overlying the arcades, defatting of the jejunal mesentery and separate dissection and ligation of the mesenteric arteries and veins to the selected segment to allow lengthening of the jejunal arcades.

In the chapter on the functional diseases of the esophagus, the authors stress that since surgery does not restore the normal motor function of the esophagus, accurate analysis of esophageal function is essential when selecting patients for operative treatment. However, the authors failed to discuss the process of investigation and selection of such patients for operation. Good descriptions of the technical aspects of surgery for esophageal diverticuli, diffuse esophageal spasm, achalasia and gastroesophageal reflux are given, but again there is little information on the pathophysiology of these conditions and virtually no discussion of the outcome of surgical management. In the section on gastroesophageal reflux and hiatus hernia, there are well-illustrated accounts of various antireflux surgical procedures. The authors favour the transabdominal approach, which I believe is the right one. It is not unusual to see patients completely free of symptoms of gastroesophageal reflux several years after a transthoracic procedure but complaining bitterly of postthoracotomy pain. The authors point out that the transthoracic approach is preferred in obese patients, in patients who have a short esophagus and in those who have recurrent gastroesophageal reflux following a previous

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CORRESPONDENCE

Classification Systems for Colorectal Carcinoma

To the editors. I read with interest Dr. Schubert's history of the evolution of classification systems for staging cancer of the rectum (*Can J Surg* 1990; 33: 8–11). He has assembled and critically analysed all of the important staging systems except the newest and most important. In 1987 a TNM (tumour–node–metastasis) staging classification was put forward with the combined efforts of the Union internationale contre le cancer (UICC)[1] and the American Joint Committee on Cancer (AJCC).[2] Table I shows the similarity between the original Dukes' stages and this classification system.

The primary purpose of a good classification system for cancer is not to ease one's memory load but to stage patients with respect to prognosis and, possibly, further treatment. An example is the subdivision of Stage III (Dukes' C) into N1 (metastases in one to three pericolic or perirectal lymph nodes) and N2 (metastases in four or more pericolic or perirectal lymph nodes). The number of lymph nodes has been shown to have prognostic importance,[3] although different break points have been used.

Table I. Combined UICC-AJCC Classification System for Staging of Colorectal Cancer Compared With Dukes' Classification*

Stage	Dukes' stage	TNM
I	A	T1N0M0
		T2N0M0
II	B	T3N0M0
		T4N0M0
III	C	T (any) N1M0
		T (any) N2M0
		T (any) N3M0
IV		T (any) N (any) M1

*UICC = Union internationale contre le cancer, AJCC = American Joint Committee on Cancer, TNM = tumour–node–metastasis.

As physicians of different disciplines and nationalities become involved in the multimodality treatment of cancer, accurate staging becomes more important. A common language must be used. The UICC/AJCC TNM system satisfies these criteria. I would encourage its use throughout Canada.

D.R. McCready, MD, FRCSC

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To the editors. Dr. McCready proposes that my article "Dukes' classification: American chaos versus British order" (*Can J Surg* 1990; 33: 8–11) omits the "newest and most important" staging system, which he refers to as the UICC/AJCC TNM (tumour–node–metastasis) classification. The English translation of the Union internationale contre le cancer (UICC) is the International Union Against Cancer. This system's classification was indeed referenced in my original article in its English translation (reference 19).

In McCready's opinion the breakdown into eight subcategories rather than Dukes' simple A, B and C classification would "stage patients with respect to prognosis and possible further treatment", and he proposes that this gargantuan system would be a better classification to use as a national policy in Canada. Indeed, this is similar to the assertion made by most of the authors of the 11 additional classification systems I have made reference to in my article. McCready's argument would be stronger if he had proof, from studies or references, that patients in each of the UICC subcategories had a significantly different prognosis or required substantially different treatment. The National Surgical Adjuvant Breast Project (NSABP), to which McCready refers, concluded that there may be a "unique Dukes' C subset of patients" with a prognosis "at least as good as Dukes' B lesions" in which there was just partial tumour penetration and "the presence of 1–4 positive nodes".[1] This article goes on to "raise serious doubts concerning the propriety of the newly proposed TNM classification schemes that fail to utilize the number of positive nodes as a predictive discriminant". It was certainly satisfying to see that the authors of this NSABP report, which represented 75 prominent Canadian and United States institutions, continued to use Dukes' nomenclature in their discussion. In their conclusions they stated, "It is neither the intent nor the desire of this report to continue the assault on the Dukes' classification, and it is quite evident that more than enough eponymous variants are in existence."

I would like to renew my plea that surgeons resist the obsession to subdivide and subcategorize and that they not be seduced into using new classification systems by phrases such and "new and improved", "newest and most impor-

tant" or even "international", unless new systems have been scientifically studied and proven superior to Dukes' classification for patient management. In Dukes' final update, he reported on a series of 2447 patients studied over 25 years.[2] I am unaware of any other study proposing a newer classification system in which such large numbers of patients have been studied and the 5-year survival has been evaluated.

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BOOK REVIEWS

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transabdominal antireflux procedure.

The book puts in one package indications, techniques and practical hints for performing a wide variety of general thoracic surgical procedures. However, it lacks description of clinical aspects, pathophysiology and investigation of the disease processes for the surgical procedures. As such, it amounts to a "how to" book. Despite these shortcomings, it will be useful to both practising general thoracic surgeons and residents.

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SURGICAL MANAGEMENT OF RHEUMATOID ARTHRITIS. Edited by F. Howard Beddow. 194 pp. Illust. Butterworths, Stoneham, Mass. 1988. $160 (US). ISBN 0-7236-1007-X

This is a valiant attempt by F. Howard Beddow, an orthopedic surgeon from Liverpool, England, to tie together the various strands in the surgical management of rheumatoid arthritis. It is based on 25 years of clinical experience and tutorials. The target audience is orthopedic surgeons-in-training. Beddow has gathered eight worthy collaborators but has done most of the work himself.

The text is divided into sections on medical management, pathologic aspects, anesthesia and the surgical management of various regions commonly affected by rheumatoid arthritis.

The section on medical management is useful for orthopedic surgeons who may not have a good working relationship with a rheumatologist. The days when rheumatologists saw their main role as protecting patients from orthopedic "knuckle-walkers" is slowly passing, but surgeons should know a little about medical management.

The section on pathologic aspects is an interesting update, but many of the old standards such as pannus invasion and the primary role of the synovium are still included. No one knows the cause of rheumatoid arthritis, but as any surgeon can attest, once all the articular cartilage is gone, that joint will never again be involved in the arthritis process.

With respect to the surgical sections, most chapters are good, especially the one on the upper limb. Soutar's section on the elbow is superb. I found the chapters on feet and hip disappointing. Almost the only forefoot operation described is excision of all the metatarsal heads, which I was taught as a resident, but which I believe has a limited role.

The hip replacement section is dated; no mention is made of noncemented hips or of modern techniques of cementing such as canal plugging, brushing, lavage and pressure injection. The vast amount of cement distal to the prosthetic tip, shown in Fig. 10.13 would do nothing to add to fixation and makes revision a nightmare. There is nothing at all on hip revision, which in Canada is now exceedingly common because many patients with rheumatoid arthritis who had their hips replaced in the early 1970s are beginning to experience loosening of the prosthesis. Infection, both in the hip and knee, is dealt with superficially.

Overall, I liked this book. Most orthopedic surgeons who look after patients with rheumatoid arthritis will find something of value in it. Although it will not replace Campbell's textbook as the bible for the orthopedic resident, this slim, 200-page book should be read by all orthopedic surgeons-in-training.

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TEXTBOOK OF LIVER AND BILIARY SURGERY. William C. Meyers and R. Scott Jones. 489 pp. Illust. J.B. Lippincott Co., Philadelphia. 1990. $99.50 (US). ISBN 0-397-50774-7

This book is intended to be a comprehensive source of information for liver and biliary tract surgeons. The 12 sections cover the development of liver and biliary surgery, anatomy, physiology, signs and symptoms of hepatobiliary disorders, radiologic and other diagnostic considerations, disorders of the liver, disorders of the biliary system, liver

continued on page 352

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Bikini Appendectomy Incision as an Alternative to the McBurney Approach for Appendicitis

Walley J. Temple, MD, FRCS, FACS

With respect to appendectomy, a surgeon's handiwork is often measured by the scar he leaves rather than by the quality of his surgery and the lifesaving judgements he makes. This is particularly true among the younger patients who spend a good deal of time in the sun, for whom some of the pleasures of an attractive physique will be marred by an abdominal scar. We tend to forget this at the start of surgery because of the overriding immediate concerns of a life-threatening problem, and we often forget it at the end of the procedure because we do not remember that it is important to leave as cosmetically attractive a scar as possible. Gynecologists have been sensitive to this need, using the Pfannenstiel incision for various pelvic operations. In this paper I describe a modified surgical approach to appendicitis — one that allows the scar to be completely hidden.

As one might guess this modified surgical approach was stimulated by experience with a patient, a 20-year-old woman who presented in the middle of the Canadian winter with a bikini tan obtained from a sojourn to the South. She was very upset over having her expensive tan ruined by emergency surgery. Hence, I named the modified incision the bikini incision.

Method

All patients whom I saw with a diagnosis of appendicitis between 1983 and 1984 are included in this report. Documentation of diagnosis, complications, technical difficulty, cosmetic results and days of hospital stay were tabulated. All but obese patients and those with signs of high retrocecal appendicitis were considered for the modified approach.

The Incision

A transverse incision is made in the superior pubic hairline through the skin and Scarpa's fascia down to the external rectal sheath (Fig. 1). The incision extends from just lateral to the midline for an average of 5 to 6 cm, as needed for subsequent exposure. A plane on the rectus fascia is easily created by sweeping the skin and subcutaneous tissues superiorly. With skin retracted the external oblique fascia is incised approximately at McBurney's point and the abdomen is entered through a standard muscle-splitting approach. Depending on the body habitus, the area exposed on the abdominal wall is slightly more medial, and adequate exposure occasionally requires the incision be extended medially into the rectus sheath. However, it is not necessary to transect the rectus muscle. If one must explore the

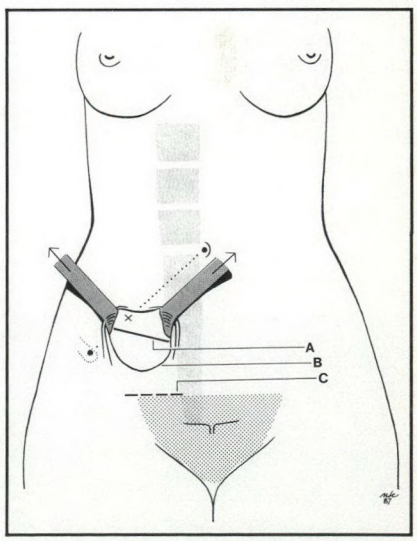

FIG. 1. Diagrammatic representation of "bikini" incision. A = muscle-splitting incision near McBurney's point on abdominal wall. B = skin incision retracted to expose McBurney's point on abdominal wall. Skin and subcutaneous tissue are easily mobilized off external oblique fascia. C = site of appendectomy incision just above pubic hairline. This is extended to expose external oblique fascia.

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abdomen through this approach, the skin incision may be extended laterally and the abdominal incision enlarged as needed. The abdominal wall is closed in a standard fashion. No drains are left in the subcutaneous tissue tunnel. Two or three chromic catgut sutures are used to approximate the subcutaneous tissue, and skin tapes are applied. When a drain is required because of an abscess it is brought out through the abdominal wall directly below the skin incision but with care taken to stay above the inguinal canal.

Results

Of 28 patients operated on for acute appendicitis, 16 (12 females, 4 males) had the modified McBurney "bikini" incision. Twelve appendices were acute or suppurative, 1 was perforated and 2 were normal. Two patients had associated abscesses that needed drainage. One normal appendix extended retrocecally about as high as the gallbladder. Three incisions were extended to assist exposure. One wound infection occurred and healed by secondary intention but without an unsightly scar. Hospital stay ranged from 3 to 14 days (median 4 days, mean 5 days). In Table I, these results are compared with those in 12 patients whose appendices were removed by the standard McBurney incision.[1] Cosmetically the pubic hairline scars were all judged as excellent and preferable to the usual paraumbilical McBurney scar (Figs. 2 and 3).

Table I. Comparison of Findings in 28 Patients Who Underwent Appendectomy Using Either the "Bikini" or McBurney Incision

Variable	Incision	
	Bikini	McBurney
No. of patients	14	12
Pathologic feature of appendix		
Acute inflammation/suppuration	12	7
Gangrene	0	1
Perforation	1	4
Abscess	2	0
Normal	2	2
Wound infection	1	1
Hospital stay, d		
Range	3 – 14	3 – 8
Mean	5	5

Comments

The bikini incision is cosmetically superior to the standard McBurney incision. It is equally safe and is not associated with an increase in complications or length of hospital stay. It is slightly more difficult to obtain adequate exposure than with the McBurney approach, but the incision can be extended for increased exposure while still resulting in a well-hidden scar. The subcutaneous tunnel and the potential for infection were not a problem. Although this incision has been used in almost every situation, it was avoided in obese patients, in those who had posterior flank signs and symptoms suggestive of a retrocecal appendix and in those who did not need a cosmetically superior incision.

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FIG. 2. Healed bikini appendectomy incision (6 weeks) at "tan line", just above pubic hair line.

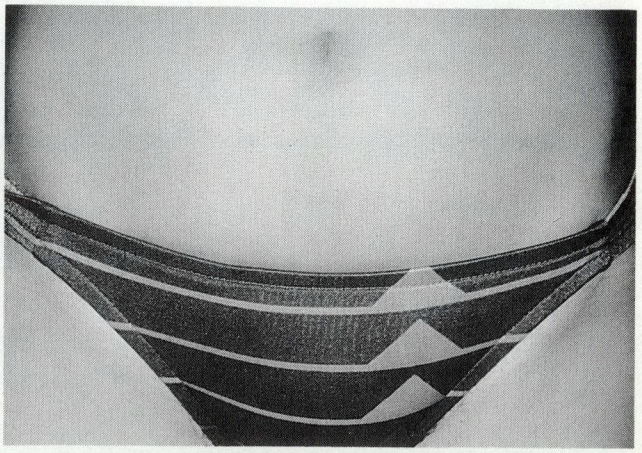

FIG. 3. Modified appendectomy incision hidden by bikini.

Presidential Address, 1989. Canadian General Surgery: Alive and Well

Fred G. Murphy, MD, FRCSC

General surgery in Canada is alive and well because general surgeons remain versatile and adaptable. If this were not the case, the specialty of general surgery would go the way of the dinosaur.

The continuing evolution of general surgery can only be maintained by reviewing the following: (a) training; (b) continuing education; (c) maintenance of competence; (d) manpower and economic aspects; and (e) interaction of general surgeons with other surgeons and specialties.

The Canadian Association of General Surgeons will continue to play a vital role in maintaining liaison between all types of general surgeons across the country and help, in any way possible, to support the ever-changing face of general surgery.

La chirurgie générale au Canada vit et se porte bien parce que le chirurgien général a su maintenir des talents variés et demeurer souple. Si cela n'était pas le cas, cette spécialité subirait le sort qu'ont connu les dinosaures.

Le maintien de l'évolution constante de la chirurgie générale dépend des facteurs suivants: (a) l'enseignement; (b) la formation continue; (c) le maintien des compétences; (d) la considération des effectifs et de l'aspect économique; et (e) l'interaction des chirurgiens généraux avec les autres chirurgiens et autres spécialités.

L'Association canadienne des chirurgiens généraux continuera de jouer un rôle vital dans le maintien d'un lien entre tous les types de chirurgiens généraux à travers le pays et aidera, dans la mesure du possible, à soutenir les virages constants de la chirurgie générale.

I can think of no greater honour and privilege than to be selected by my peers to be your president. As you know, our society is relatively young, being 12 years old, but when I review the list of past presidents, I feel most proud that my name would be associated with such distinguished surgeons. This year, Dr. Bruce Tovee, our second president, passed away, and I think it is appropriate to bring his death to the attention of our association. It is because of such men as Dr. Tovee that our society, which brings together general surgeons from all over Canada, is in existence. My year as president has been an excellent learning experience, and had it not been for the helpful people about me — the executive, the committee chairmen and the executive director — I would have found this an insurmountable task. My wife, too, always managed to correlate my personal and working life to allow me to attend meetings, conferences and teleconferences.

One of the privileges the president of the association has is to address you. This meant reviewing other presidential addresses, which, generally, carry a message or give an overview of the "state of the union" for the year. After practising general surgery in a community hospital for 30 years, I have found that one of the most persistent, recurrent complaints is that general surgery is a disappearing specialty and that it is being hacked and dismembered, piece by piece, from inside, from outside, from top to bottom, so that soon there will be no specialty of general surgery. My good friend Dr. Roy from Quebec has even provided an obituary that was prepared for the Province of Quebec. Fortunately, as with political forecasts, it should be taken with a grain of salt. It is my own feeling that, rather than becoming extinct like the dinosaur, we are an extremely active, adaptable, versatile and vital group of first-line surgeons. As many of you know, one of my favourite pastimes is fishing for Atlantic salmon. Just as salmon fishing is the king of sport fishing, so, also, general surgery is the king of surgery because both, in their own way, share unparalleled excitement, anticipation and reward.

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In the large centres, as Dr. Langer noted last year,[1] the importance of surgical research and the results of research done by surgeons through the years has been tremendous. Surgical research must be encouraged and kept moving forward. At the other end of the scale, the king of the castle in small community hospitals is the general surgeon. He has to be extremely adaptable — he has a type of practice that very few of us can perform. Personally, I practise in a medium-sized, hospital with more than 500 beds and, having met surgeons at both ends of the scale, I realize how few of us, after we have been in practice for 5 to 10 years, could substitute for one another. Consequently, it is important that, as a group, we have a deep, mutual respect for the type of practice which each association member has in this wide country. We must never forget that Canada starts at Newfoundland and extends through to Victoria, that the physical layout of Canada is such that centralization of services is not feasible. It must also be realized that lay people and politicians have dictated to physicians and surgeons much of how and where medical services will be made available. Therefore, even though medical personnel have input into what is or is not ideal, we must accept that we are not the masters of our house, that our houses are provided by the people of our country through the government, and we must make every effort to provide the best possible surgical service for all arenas.

This leads to the many facets of surgical practice which the Canadian Association of General Surgeons (CAGS) can influence through the activity of its members. It is important that more members from all areas and types of practice should volunteer their services to help elucidate the problems that face surgery today, in order to keep it alive and well.

I have considered several parameters upon which I intend to enlarge, which will help to keep us, as surgical leaders, viable, adaptable and versatile. These are: (a) the training of surgeons; (b) the continuing education of surgeons; (c) the maintenance of competence; (d) manpower and economic aspects; (e) the interaction between general surgeons and other surgeons and physicians.

Training of Surgeons

The training for general surgery has just been extended to 5 years by the Royal College of Physicians and Surgeons of Canada. Indeed, it shows that the field of general surgery is not shrinking but, rather, it is expanding to the point where it needs more time for training than ever before. I would like to see at least 1 of these 5 years spent in surgical research, and the program of surgical research should be set so that it would be worthwhile to the nation and to surgeons in training in the development new technology and furthering medical progress. Also, equally important, the resident or fellow should be encouraged to develop a truly analytical mind. It is much too common in other specialties to have a sort of knee-jerk reaction to medical care, and the first thing reached for is another test, with an appropriate arrow pointing to the next step, to another arrow, to the next step. As Ravitch suggests, the surgeon becomes the end organ of some cerebral synapse elsewhere.[2]

I believe that a deductive type of thinking and logical process from a mind that has been helped by research to understand pathophysiologic processes will help to prevent that mind from developing a "lazy brain syndrome". It will also help develop a continuing, self-critical mind which keeps the surgeon learning through his or her lifetime. As Thomas Carlyle wrote: "the greatest of all faults is to be conscious of none". All too often, I get a pert answer from a young intern who says that even though the patient looks like a facies of Hamilton Bailey's *Textbook of Surgery*, his x, y and z tests are normal; therefore, the patient must be all right. I think that a well-trained surgeon must be a well-thinking surgeon, and there is no better place than a year or so of thoughtful and worthwhile research.

The other aspect of a 5-year training program is that all program directors and chairmen of the departments must, at all cost, consider the primary purpose of a residency program to be education of the resident and not service to the hospital. Frank C. Spencer has elicited some aspects of residency training, stating that (a) the primary purpose is education, (b) the on-call time must be reasonable and (c) the number of hours spent in "scut work" must be kept well under control.[3] Thus, the extra time would be used to train a better surgeon and not to keep the appropriate manpower in the service of the program itself. As I listen to many general surgeons across Canada, I realize that it would be impossible to train every surgeon for every situation for every hospital size in our country.

It seems to me that after some "core training", there should be a trend to three types of general surgeon. One type would practise in a large teaching hospital and would require extra training in his or her special interest of surgery. Such a surgeon would become a leader in that particular aspect of general surgery. A second type would be the general surgeon in a medium-

sized hospital who should be able to add to the surgical services provided by having a certificate of special competence or accreditation without certification in such fields as thoracic, vascular and head and neck surgery, surgical oncology, critical care and trauma, thus enhancing the overall care of people in the region served. The third type would be a surgeon in a smaller hospital, who must have a good, broad basis with a thinking, deductive surgical mind, who soon learns his abilities and capabilities, his inabilities and his limitations, so that he can handle well the problems within his scope but recognizes quickly the ones with which he needs further help. Again, an organization such as CAGS should be able to cement relationships among surgeons at various levels of hospitals and surgical care. It should always be considered an honour for any surgeon to be consulted by another surgeon for special expertise and help.

It is apparent that, after practising for many years, the surgeon tends to develop a certain degree of tunnel vision as to the best type of surgery and practice — that theirs is the one and only type — and to feel sorry for the surgeon who is in a larger or smaller centre, who just doesn't know what the real world is like. It might be conceived that many young surgical residents feel insecure in leaving the large centre, and it is suggested that the "role model" for surgeons to go out into smaller communities where the need is the greatest is not seen these large centres. Serious consideration must be given to a rotation, of a reasonable period of time, to community hospitals to see what that type of surgical practice is like. Paul A. Ebert stated recently that "we continue to ask ourselves why subspecialization has become so popular, especially in general surgery".[4] He stated that "it is only normal for students to imitate their teachers". I think that anybody who trained in Montreal during the time of the late Dr. John Armour would have recognized his residents at the dining table because within weeks they had the same fiery lines and the same mannerisms as their chief, and these lasted through their whole residency. So contact with a "role model" seems essential in the enticement of general surgeons to communities where there is an acute shortage.

To all young surgeons, a word of wisdom written in 1711 by Alexander Pope: "be not the first by whom the new is tried nor yet the last to lay the old aside";[5] or, as stated by another: "there are two types of fools; one says 'this is old and therefore is good'; the other says 'this is new and therefore better'."

Continuing Education of Surgeons

I feel that a well-trained general surgeon in a good surgical program must get the impetus to continue his education, and I think that CAGS has shown itself to be a leader among the national specialty societies that meet in conjunction with the Royal College meeting; CAGS produces a worthwhile program that is informative and stimulates continuing education. The unfortunate fact is that there are many members of our association who do not attend. I am sure that they must attend meetings elsewhere. It is my opinion that our meetings should be across the nation, as they have been, so that easterners who refuse to go west and westerners who refuse to go east get a chance to attend our meetings. The education committee, in the past and at present, has done a tremendous job. The postgraduate courses have been increasing in attendance each year, and continuing education will keep general surgeons from becoming an endangered species. In the future CAGS may sponsor regional courses.

Maintenance of Competence

This is a question which CAGS must address. Already, the Royal College is becoming involved. Maintenance of competence is, at present, a touchy political issue, but some realize that if surgeons do not become involved, then other groups, other people and other agents will become involved. I think that all of us, as we practise over the years, perform fewer procedures more often as we abandon one part of the body because of special interest in another part. Though we have much in common, we also have much not in common; therefore, it seems appropriate to me that, when this form of maintaining competence is programmed, each surgeon will have to identify in which aspect of medical and surgical practice he wishes to be considered competent. I agree that the basic aspect of surgery is common to all, but the search for a parathyroid tumour might interest only a very small percentage of us here today. The management of thoracic outlet syndromes would interest an even smaller percentage, so I see this as a very important, but complicated, problem which is going to be in the forefront of both the Royal College and our association in the ensuing years.

Manpower and Economic Aspects

The manpower problem in Canada has been more than amply covered in other presidential addresses.

There is an acute shortage of general surgeons in Canada, and surgeons have been criticized for leaving general surgery and going into the more glamorous subspecialties. I realize that, at least, there is a maldistribution of general surgeons. Also, I am sure that subspecialization is a universal trend in all medical practices and that there is a certain desire to know more about a little throughout the medical field. This is not a bad concept. I believe that surgeons have done this of their own volition because of the type of practice that they feel they would be most comfortable doing. I have referred to some manpower problems along with those of training in my discussions with those who have practised in large communities with modern facilities and then have gone to the far north or the far east and have been astonished at how quickly they needed to go back to their basic training to manage the new type of practice they have encountered.

Economics is also considered to be a factor associated with manpower. I do not need to tell everyone here today that for what we do and the responsibilities and intensity of our work, we are not economically rewarded. Some of my old surgical friends have said to me that young, smart practitioners who have decided to go back to specialize told them: "I like what you do in general surgery, but no way am I going to suffer the anxieties brought on by the tenseness of the work, the long hours of the work, for the economic return, when so many other specialties have a much better lifestyle and a much better economic return." Saints and martyrs are good people, but they are not as popular as they once were. I think that this is probably a universal problem across our nation. The ongoing committee in CAGS has been working towards evaluating this problem.

Interaction Between General Surgeons and Other Surgeons and Physicians

There is continual interaction between the practice of general surgery, other surgical subspecialties and physicians. Reviewing some of the recent presidential addresses of other societies, it is interesting to note that paranoia runs high at times. One of the main problems in general surgery is the attitude of general surgeons. The general surgeons seem to be thrilled by doing the biggest and most difficult procedures in their area of practice or interest. They have, through the years, developed diagnostic procedures which have been beneficial, but because they were more mundane, they have let them trickle off to their physician friends. For example, the diagnostic procedures associated with arteriography have been gladly referred to our radiology friends, who now do them better. When a field is given up, control over further developments is also surrendered, so that we now have interventional radiologists who suggest that a second opinion be obtained by them as to which vascular problems should be managed by the surgeon. Another example is the field of endoscopy. Here CAGS has done a tremendous job to maintain endoscopy in the field of surgical training. However, the therapeutic aspect of endoscopy is not pursued by all surgeons. Young surgeons and those in training should make every effort to keep up with and look into the future of such "mundane procedures". It is very easy to abandon a railway track, but it is nearly impossible to have it rebuilt; therefore, surgeons should take a keen interest in what they are abandoning.

The other interaction, of course, is between general surgeons and subspecialist or superspecialist groups. It seems that in medical schools students have been taught that some diseases and treatments which general surgeons believe belong in their field belong to a subspecialist group. The solution here is that whatever a general surgeon decides to do in the area in which he practises, he must do well, he must keep up to date, be respected and maintain overall competence to win out eventually. Many of the diseases treated by general surgeons 30 years ago have been abandoned, and this is kept foremost in our minds; however, there are many new procedures, new developments and new techniques which, if we maintain our adaptability and versatility, will ensure that we will not become dinosaurs. This cannot be accomplished without a vibrant society like ours and a great deal of personal effort by the general surgeon. The avoidance of a "lazy brain syndrome", by maintaining a logical and self-critical mind, will and must prevail.

And so not to get caught up in too many words, again I refer to Alexander Pope:[6] "Words are like leaves; and when they most abound much fruit of sense beneath is rarely found."

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Early Gastric Cancer: Is It a Distinct Clinical Entity?

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Of 199 patients with gastric cancer seen at The Montreal General Hospital between 1970 and 1981, 104 were considered to have had a curative resection, and 26 of these were early gastric cancers (EGC). The authors compared early gastric cancers with advanced, but resectable, gastric cancers to determine whether EGC is a distinct entity or a stage in the progressive evolution of gastric cancer. They found that depth of invasion was the primary determinant of outcome, but that there was no discrete cut-off point between the depth of invasion associated with early and with advanced gastric cancers. The pathological features normally associated with a favourable prognosis in gastric cancer, such as absence of lymph-node metastases, an expanding growth pattern, intestinal metaplasia, and well-differentiated histologic features correlated highly with depth of invasion but did not appear to change abruptly between EGC and advanced resectable lesions.

The authors conclude that EGC is not a distinct pathological or clinical entity but a stage in the progressive growth of gastric cancer.

Des 199 patients souffrant d'un cancer gastrique vus à l'Hôpital général de Montréal entre 1970 et 1981, 104 ont subi une résection jugée curative, et 26 de ceux-ci étaient porteurs de cancers gastriques précoces (CGP). Les auteurs ont comparé les cancers gastriques précoces et les cancers gastriques avancés mais résécables afin de déterminer si les CGP représentent une entité distincte ou un stade dans l'évolution du cancer gastrique. Ils ont observé que la profondeur d'envahissement constitue le premier déterminant de l'issue de la maladie mais ils n'ont pu établir de profondeur critique permettant de distinguer cancers gastriques précoces et avancés. Les caractéristiques pathologiques normalement associées à un pronostic favorable telles que l'absence de métastases des ganglions lymphatiques, de caractéristiques d'évolution, de métaplasie intestinale, et les caractéristiques histologiques de différenciation offraient une forte corrélation avec la profondeur d'envahissement mais elles ne paraissaient pas changer brusquement entre les CGP et les lésions résécables avancées.

Les auteurs concluent que les CGP ne représentent pas une entité pathologique ou clinique distincte mais un stade de l'évolution du cancer gastrique.

Early gastric cancer (EGC), defined as a tumour confined to the mucosa or submucosa of the stomach with or without nodal metastases,[1,2] is being diagnosed more frequently because of the increased availability and accuracy of diagnostic techniques.

Since EGC was established as a distinct lesion, the remainder of gastric malignant tumours have been referred to as advanced gastric cancers.[1-3] Many regard EGC as a distinct clinical entity.[4] The question of whether it is a distinct entity or merely an earlier stage in the evolution of gastric cancer has not been resolved.

We carried out a retrospective study of gastric cancer at The Montreal General Hospital over the 11-year period from 1970 to 1981 to assess our total experience with gastric cancer. From this study we were able to compare EGC with the more advanced forms. If early gastric cancer were truly a distinct entity, one would expect a distinct fall-off in survival and in those pathological features known to be associated with a favourable prognosis when EGC is compared to advanced, but resectable, gastric cancer. Such pathological features include absence of lymph-node metastases, well-differentiated histologic features, presence of intestinal metaplasia in the gastric mucosa and an expanding pattern of tumour growth.[5]

Patients and Methods

The clinical and pathological features of 199 gastric carcinomas diagnosed at The Montreal General Hospital between 1970 and 1981 were documented. Tumours were diagnosed by x-ray studies or endoscopy, or both. If surgery was carried out, the type and extent of the operation were noted. A judgement was made as to whether the procedure was considered curative or palliative by the operating sur-

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geon. All patients had a pathological diagnosis of gastric cancer, and pathology reports were reviewed and histological sections re-examined by a single pathologist to establish the site, morphologic findings, depth of invasion and the presence or absence of lymph-node metastases in each case. The degree of tumour differentiation was recorded and the pattern of tumour growth, either expanding or infiltrating, was noted. In addition, the presence or absence of intestinal metaplasia in the gastric mucosa at a distance from the tumour itself was evaluated. Metaplasia was considered to be absent if the change was either absent or minimal, and present when the metaplastic change was moderate or marked.

As a means of comparing EGC with advanced gastric cancer, the primary tumours were classified by level according to the depth of penetration of the stomach wall as follows: A, tumours involving the lamina propria only; B, submucosal invasion; C, invasion into, but not through, the muscularis propria; and D invasion through the entire gastric wall. Levels A and B tumours were considered as EGC and C and D as advanced disease.

All patients were followed up for at least 5 years or until death. Actuarial survival was calculated from the data for each level of invasion of the primary tumour, and for the group as a whole. Linear regression analysis was then used to test for a linear relation between depth of tumour invasion and survival, lymph-node involvement, tumour differentiation, intestinal metaplasia and tumour growth pattern. Data were considered statistically significant when $p \leq 0.05$.

Findings

Of the 199 patients examined, 26 had EGC. Twenty-one patients had no operation and 74 were considered to have had palliative procedures; the remaining 104 patients, including all those who had EGC, were considered to have had potentially curative operations.

Demographics

The patients ranged in age from 26 to 90 years (mean 65 years) and there was no significant difference in the mean age between those with EGC and advanced resectable gastric cancers. Superficial tumours tended to be diagnosed with equal frequency in men and women, but more deeply invading lesions were more likely to be diagnosed in men (Table I).

Location

The distribution of tumours within the stomach was similar for both early and advanced cancers, except for a slightly increased likelihood of proximal gastric cancers in patients with more advanced tumours (Table II).

Pathological Features

The degree of tumour differentiation is shown in relation to depth of invasion in Fig. 1. Tumours tended to be progressively more poorly differentiated at deeper levels of penetration, but there was no abrupt change between the early and advanced tumours. Depth of invasion correlated highly with tumour differentiation ($r = 0.99$, $p < 0.01$).

The relationships between depth of invasion and pathological features of intestinal metaplasia, tumour growth pattern and lymph-node metastases are shown in Fig. 2. There was a highly correlated linear relation between depth of invasion and each of these features (intestinal metaplasia: $r = 0.98$, $p < 0.01$; tumour growth pattern: $r = 0.98$, $p < 0.01$; lymph-node metastases: $r = 0.98$, $p < 0.01$). Lymph-node involvement increased progressively with the level of invasion. No nodal involvement was seen unless the primary tumour had penetrated deep to the muscularis mucosae. If patients with levels A, B and

Table I. Age and Sex Distribution of 104 Gastric Cancers According to Level of Invasion

Level	Mean age, yr	Male, no.	Female, no.
A	66	5	6
B	64	8	7
C	60	13	7
D	67	42	16

Table II. Location of Tumours in Early Gastric Cancer (EGC) and Advanced Gastric Cancer

Location	Early, %	Advanced, %
Proximal	12	26
Body	27	24
Distal	61	50

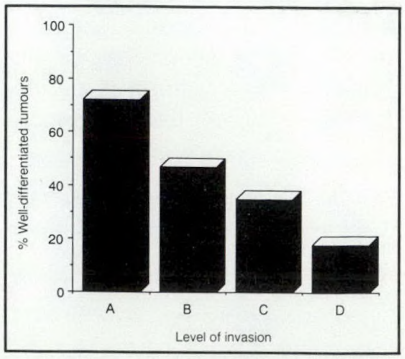

FIG. 1. Percentage of patients with histologically well-differentiated tumours, according to level of invasion.

C are pooled together, the survival was not affected by the lymph-node status of the patient. Patients with lymph-node involvement had a mean survival (± SEM) of 4.25 ± 0.47 years, compared with 4.44 ± 0.22 years in those without nodal metastases. Even in level D patients, survival was 2.89 ± 0.32 years when nodes were involved with tumour compared with 2.94 ± 0.41 years in patients without nodal metastases.

Surgical Procedures

The type of operation used in the 104 patients operated upon for cure is shown in Table III. Total gastrectomy was not required for the resection of EGC in this study.

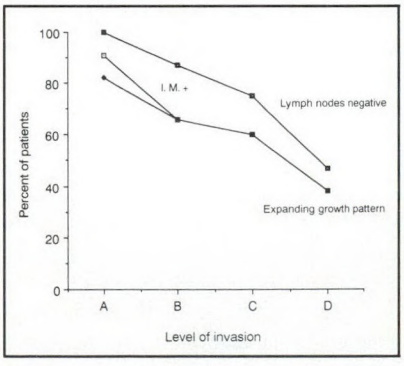

FIG. 2. Percentage of patients with intestinal metaplasia (I.M.+), expanding pattern of tumour growth (Exp) and absence of lymph-node metastases, according to level of invasion.

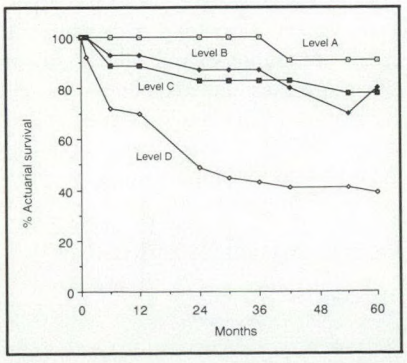

FIG. 3. Actuarial survival rates from time of surgery, according to level of invasion.

Survival

Actuarial 5-year survival was also seen to decrease with depth of invasion (Fig. 3). There was little difference in survival curves between levels A, B and C. Levels A and B are considered "early" gastric cancers, whereas level C is not. The only appreciable fall off in survival was seen with level D tumours.

Four of 26 patients with EGC failed to survive 5 years. One (level B) died of metastatic carcinoma. The others died of unknown causes, although one was known to have had a metastatic renal cell carcinoma at the time of operation. One of two patients with EGC who had lymph-node involvement survived; the other had associated metastatic renal cell carcinoma. Three of five level C patients with nodal involvement survived, a rate similar to that observed in patients without nodal involvement. Ten of 31 level D patients with lymph-node involvement lived 5 years, a survival rate only marginally worse than that for patients who were free of involved nodes.

Discussion

From this study it appears that gastric cancer begins in the mucosa of the stomach and progresses in a relatively orderly fashion through the gastric wall. The earliest lesions involve the lamina propria only and are infrequently associated with lymph-node involvement. Excision of these lesions results in cure in a high percentage of cases. Nodal involvement is more frequent as tumours invade the submucosa,[6,7] and is increasingly likely as the primary tumour invades the gastric wall more deeply.

Intestinal metaplasia, histologically well-differentiated tumours and an expanding growth pattern have previously been shown to be associated with a good prognosis in patients with gastric cancer.[5] We found these favourable pathological features to be present in a high proportion of patients with EGC, but less evident as depth of tumour invasion progressed. Furthermore, there was a progressive gradual increase in the likelihood of lymph-node metastases and a concomitant decrease in survival as tumour invasion progressed. All these changes occurred in a linear or progressive fashion with increasing depth of tumour invasion, without any discernible cut-off to distinguish early from advanced gastric cancer. The survival curves were also found to be linear and not biphasic. These data suggest that to segregate those lesions called EGC as a distinct entity would be an arbitrary distinction, rather than one based on biologic behaviour. Gastric cancers do not appear to behave any differently from colonic cancers when depth of invasion in the wall of the bowel is an important determinant of outcome, but early colonic cancer has not been designated a distinct entity, except in the case of polyps.

It has been suggested[4] that the depth of gastric wall invasion, and not metastases to regional lymph nodes, appears to be the primary determinant of prognosis in gastric cancer. Our data certainly support this concept. Although we found an

Table III. Surgical Procedures Performed in Patients With EGC and Advanced Gastric Cancer

Procedure	Early no.	Advanced no.
Partial gastrectomy	23	51
Total gastrectomy	0	11
Esophagogastrectomy	3	16

increasing incidence of lymph-node involvement with increasing depth of invasion, there was no demonstrable difference in survival, at each level, whether or not nodes were involved.

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BOOK REVIEWS

continued from page 340

resection, transplantation, hepatobiliary trauma, diseases of infancy and childhood, and liver and biliary diseases in pregnancy. The largest sections are those covering disorders of the liver and the biliary system, which are divided into separate chapters covering different entities.

This readable, well-written book has a consistent style, is accurate and up to date and contains many useful illustrations. Another good feature is that the bibliography is organized into separate sections following each chapter. This allows the researcher to pursue certain topics in detail. The references are to current as well as classic and historical articles.

The first chapter, which is dedicated to the development of liver and biliary surgery, gives a historical review of how this subspecialty evolved. The chapter on anatomy is well illustrated and the important features of the surgical anatomy of the liver as described by Couinaud are considered. In the chapter on liver resection the use of the ultrasonic dissector is discussed.

Although this book is shorter than Blumgart's extensive, classic, two-volume *Surgery of the Liver and Biliary Tract,* it covers the subject matter in a concise, yet complete manner.

I highly recommend this book for all serious practitioners of hepatobiliary surgery. For students and residents it provides sufficient information presented in a concise but highly readable and consistent style. For more senior practitioners it summarizes the topics well and provides an organized bibliography that can be used as a basis for further reading and research. It is a must for university and hospital libraries.

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AN ATLAS OF SURGICAL EXPOSURES OF THE UPPER EXTREMITY. Raoul Tubiana, Christopher J. McCullough and Alain C. Masquelet. Illustrations by Léon Dorn. 359 pp. Illust. J.B. Lippincott Co., Philadelphia. 1990. Price not stated. ISBN 0-397-58316-8

This beautifully illustrated atlas represents a notable contribution to the literature on upper extremity surgery. The great strength of this work is the quality, clarity and accuracy of Dorn's artwork. There clearly has been close collaboration between the surgeon-authors and their illustrator. The atlas is organized along anatomic lines with additional chapters focusing on exposure of peripheral nerves, arteries and veins, Dupuytren's contracture, infections, compartment syndromes and skin flaps.

The introduction is succinct and contains many gems that are universally applicable to upper extremity exposures. Each exposure is discussed according to its indications, the patient's position, the incision and the details of the exposure. In general the chapters are comprehensive, although the anterior exposure of the elbow is not discussed, nor are there detailed instructions on reattachment of the triceps after its reflection from the olecranon. One might also question the utility of including an axillary approach to the shoulder joint as a method of treating shoulder instability, a subdeltoid approach to the proximal humerus and the use of an oblique dorsal skin incision to expose the scaphoid and the lunate. The chapters are not referenced, although a list of selected references is included at the end of the book. The chapters organized along nonanatomic lines (i.e., compartment syndromes) would, in particular, benefit from more extensive referencing.

Although some fault may be found with certain segments of the text the overwhelming strength of the illustrations makes this a very worthy volume. Trainees, in particular, will find the lavish illustrations especially useful in enhancing their understanding of surgical anatomy. This book deserves a place in the library of every institution and individual performing any type of upper extremity surgery.

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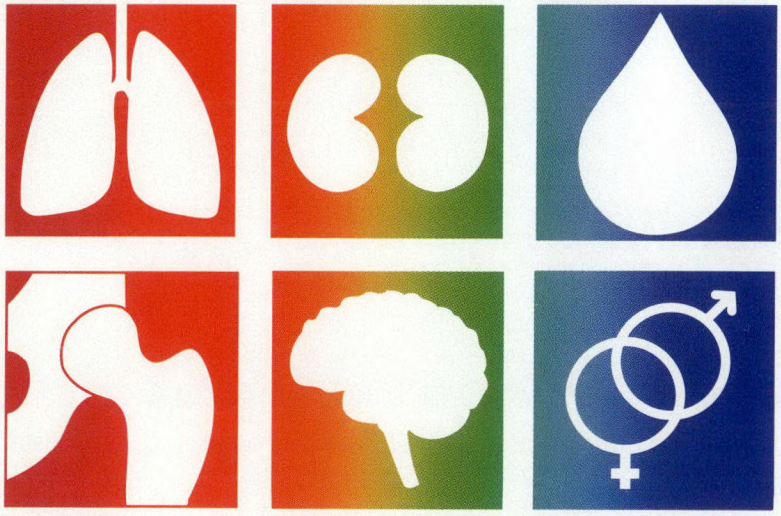

Bone/Skin
90.3%
(n=1208)

Meningitis
88.7%
(n=1378)

STD *(N. gonorrhoeae)*
98.9%
(n=2711)

(Adapted from Hell K.[1])

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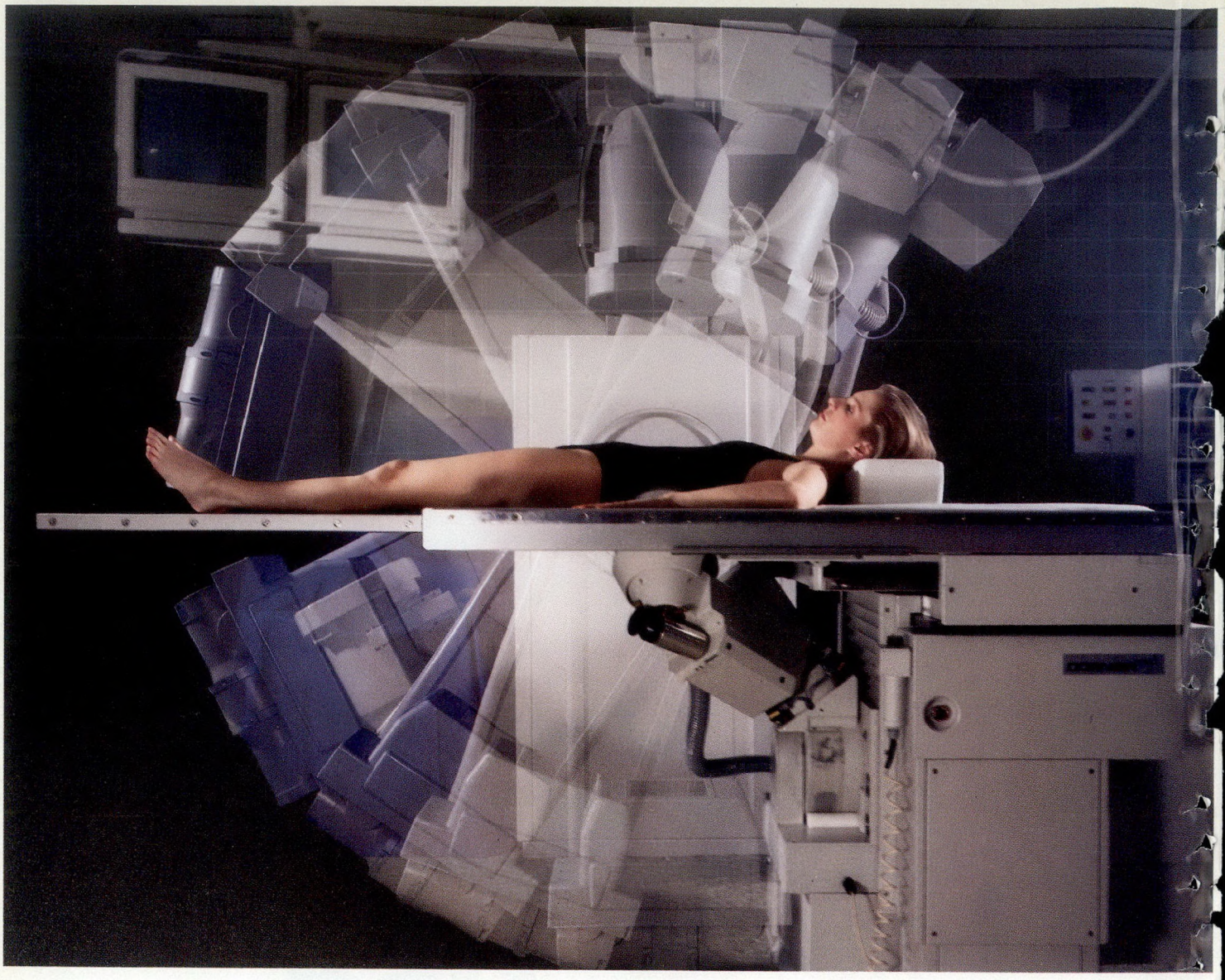

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Management of Pyogenic Liver Abscess in the Era of Computed Tomography

Carol J. Swallow, MD;* Ori D. Rotstein, MD, FRCSC

The advent of high-resolution imaging has allowed earlier diagnosis of pyogenic liver abscess. Because radiologically guided percutaneous drainage (PCD) of liver abscesses is controversial, the authors studied 40 patients with liver abscess admitted to the Toronto Hospital between 1982 and 1987 to determine the role of PCD versus operative drainage (OD). The diagnosis of pyogenic liver abscess was made at autopsy (4 patients), at laparotomy (6) or by radiologically guided aspiration of pus (30). Ultrasonography and computed tomography were highly sensitive (85% and 96% respectively) in detecting liver abscess.

Of the 36 patients treated for liver abscess all received antibiotics intravenously; 31 also underwent a drainage procedure. Treatment with antibiotics alone was associated with a success rate of 80% and a death rate of 20%. The success rate for those who had PCD was 75% with a death rate of 13%; 2 patients in this group of 16 subsequently required OD for cure. In the 15 patients initially treated with OD, success and death rates were 87% and 13% respectively. For solitary abscesses, success rates were comparable for PCD and OD (86% and 90% respectively). For unilobar multiple abscesses the success rate was 100% for both PCD and OD, but for bilobar multiple abscesses the rates were only 40% and 67% respectively. Complication rates were similar for both methods of drainage. The authors conclude that pyogenic liver abscess can now be safely and efficaciously managed with a combination of antibiotics and PCD.

La venue des techniques d'imagerie à haute résolution ont permis un diagnostic plus précoce des abcès hépatiques pyogènes. Comme le drainage percutané (DPC) des abcès hépatiques sous contrôle radiologique est contesté, les auteurs ont étudié 40 patients qui ont été reçus à l'Hôpital de Toronto entre 1982 et 1987, afin de déterminer quel est le rôle du DPC par rapport au drainage opératoire (DO). Le diagnostic d'abcès hépatique pyogène fut établi à l'autopsie (4 patients), à la laparotomie (6) ou par aspiration de pus sous contrôle radiologique (30). L'échographie et la tomographie axiale ont été très sensibles (85% et 96% respectivement) pour déceler les abcès hépatiques.

Les 36 patients qui furent traités pour abcès hépatiques reçurent tous une antibiothérapie intraveineuse; 31 eurent aussi un drainage. L'antibiothérapie seule eut un taux de guérison de 80% et une mortalité de 20%. Le taux de succès de ceux qui eurent un DPC fut de 75% et la mortalité de 13%; 2 des 16 patients de ce groupe nécessitèrent un DO pour assurer la guérison. Des 15 patients initialement traités par DO, les taux de guérison et de mortalité ont été, respectivement, de 87% et de 13%. Dans les cas d'abcès solitaires, les taux de guérison étaient comparables pour le DPC et le DO (86% et 90%). Dans les cas d'abcès unilobaires multiples, le taux de guérison fut de 100% aussi bien pour le DPC que pour le DO; toutefois, pour les abcès bilobaires multiples, les taux de guérison furent de 40% et de 67%, respectivement. Les taux de complications furent similaires pour les deux méthodes de drainage. Les auteurs concluent que les abcès hépatiques peuvent maintenant être traités de façon sûre et efficace en associant antibiothérapie et DPC.

In their classic paper published in 1938, Ochsner, DeBakey and Murray[1] reported a 78% death rate in patients with pyogenic liver abscess. Over the ensuing decades, despite the introduction of broad-spectrum antibiotics, death rates remained as high as 70% in unselected series.[2-5] The advent of more sophisticated imaging techniques in the 1980s has facilitated earlier diagnosis of liver abscesses, and the death rate has concomitantly been reduced to between 11% and 21%.[6-9]

Current controversy over the management of pyogenic liver abscesses is focussed on the optimal technique of abscess drainage, that is the role of operative drainage (OD) versus percutaneous drainage (PCD). From the Mayo Clinic series published in 1986[6] it was concluded that PCD should be the initial drainage procedure when no concomitant surgery is planned. By contrast, Klatchko and Schwartz[8] concluded that "surgical drainage remains the standard" initial management because of a high initial failure rate in patients treated by PCD.

The purpose of our study was to review the management and outcome of patients who had a diagnosis of pyogenic liver abscess after the introduction of computed tomography (CT) in our institution,

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particularly with respect to the role of PCD.

Methods

The charts of all 40 patients who had a final diagnosis of pyogenic liver abscess at the Toronto Hospital between January 1982 and December 1987 were reviewed. The diagnosis was confirmed at autopsy, at laparotomy, or by radiologically guided aspiration. The criterion for a diagnosis of pyogenic abscess was aspiration of purulent material but not necessarily a positive result on Gram's staining or culture of the abscess contents. Amoebic abscesses were excluded. For PCD, a no. 10 to 18 French catheter was inserted by the Seldinger technique under local anesthesia and connected to closed suction drainage. Frequent follow-up imaging was done to ensure adequacy of drainage. For OD, needle aspiration was used to locate abscesses not apparent from the surface of the liver. Abscesses were widely unroofed, loculations were broken down and a soft drain was left in the cavity; earlier in the study open drainage was often used, but recently closed suction drainage has been used exclusively. Data were collected on patient and abscess characterisics, diagnosis, treatment, outcome and duration of hospital stay.

Findings

Patient Characteristics

The 40 patients ranged in age from 20 to 91 years (median 63 years). The male to female ratio was 26:14, a finding typical of most reported series.[4,8–10] The median duration of symptoms before diagnosis was 11.5 days. In 23 of the 36 patients who were treated for liver abscess, the diagnosis was not made before admission; for them the mean duration of hospitalization from the time of admission to diagnosis was 1 day for those admitted to medical wards (12 patients) and 2 days for those admitted to surgical wards (11). The diagnosis was made at autopsy in 4 patients, at laparotomy in 6 and radiologically, based on aspiration of pus from the identified lesion, in 30.

Etiology

The most common source of infection was the biliary tree (15 patients); spread by way of the portal vein, chiefly due to diverticulitis, was second in frequency (8 patients). In five patients, liver abscesses were judged to be secondary to disseminated septicemia with bacteria (three) or fungi (two). Liver abscesses developed in two patients after blunt trauma. One had a hydatid cyst which became secondarily infected. Twenty percent of abscesses were cryptogenic, a rate consistent with that reported in recent series.[6–9,11–13]

Clinical Presentation

As has been reported in most series, symptoms fell into three main categories (Table I). Constitutional symptoms included fever and anorexia in 73% and 50% of patients, respectively. Abdominal symptoms consisted chiefly of epigastric or right upper quadrant pain, or both, which was present in 53% of patients. Chest symptoms were reported by a small group of patients. Physical findings fell into the same three categories. Three-quarters of the patients had a documented fever with a body temperature greater than 38°C. The most common abdominal findings were tenderness and hepatomegaly, although these were found in only 58% and 35% of patients, respectively. Only 15% of patients presented with abdominal pain, tenderness, hepatomegaly and fever, a clinical complex considered classic for pyogenic liver abscess.

Laboratory Findings

The leukocyte count was elevated in 73% of patients, and individual liver function test (LFT) results were elevated in up to 85% (Table II). To determine whether underlying biliary tract disease *per se* was responsible for the elevation in LFTs, patients with biliary versus nonbiliary sources of infection were compared. For each LFT evaluated, at least 50% of the abnormal values occurred in patients whose liver abscess was nonbiliary in origin. These data suggest that pyogenic liver abscess *per se* can cause an elevation of LFT values, but that the diagnosis of liver abscess cannot be ruled out if the LFT results are normal. From the lack of sensi-

Table I. Clinical Presentation

Symptom/sign	No. (%)
Fever and/or chills	29 (73)
Anorexia, with or without weight loss	20 (50)
General malaise	16 (40)
Abdominal pain	21 (53)
Nausea/vomiting	2 (5)
Chest pain	5 (13)
Dyspnea	4 (10)
Cough	1 (3)
Shoulder pain	1 (3)
Severe headache	1 (3)
Asymptomatic	1 (3)
Fever (> 38°C)	30 (75)
Jaundice	11 (28)
Lowered level of consciousness	12 (30)
Weakness/lethargy	3 (8)
Systolic blood pressure < 90 mm Hg	10 (25)
Abdominal tenderness	23 (58)
Hepatomegaly	14 (35)
Abdominal mass	2 (5)
Decreased chest expansion	6 (15)
Chest tenderness	2 (5)
Elevated hemidiaphragm	1 (3)
Hypothermia	1 (3)
Grand mal seizures	1 (3)

tivity and specificity of symptomatic complaints, physical examination and laboratory findings, it is evident that clinical presentation is unreliable in the diagnosis of liver abscess.

Imaging Studies

The most useful radiologic modalities for detecting pyogenic liver abscesses were ultrasonography (US) and computed tomography (CT). Ultrasonography identified abscesses in 81% of patients (25 of 31), whereas CT was more sensitive, identifying abscesses in 96% of patients (24 of 25). The diagnosis was made at laparotomy in one patient whose abscess was not detected on CT. In those with multiple abscesses, both US and CT were sensitive in detecting the multiplicity (13 of 16, and 12 of 13 patients, respectively). A chest x-ray film was insensitive, showing an abnormality in only 28% of patients. Liver/spleen scanning and angiography were done in seven and three patients, respectively, and were positive in all. However, all of these patients also had a positive US or CT scan.

Table II. Selected Laboratory Data

Measurement	No./no. tested (%)
Leukocyte count, > 10.0 X 10^9/L	29/40 (73)
Bilirubin, > 20 μmol/L	19/39 (49)
Alkaline phosphatase, > 100 U/L	34/40 (85)
Serum aspartate transferase, > 40 U/L	21/36 (58)
Prothrombin time, > 2 s over control	11/33 (33)
Partial thromboplastin time, > 5 s over control	9/33 (27)

Abscess Characteristics

The incidence of single versus multiple abscesses was approximately equal; 21 patients had single abscesses (17 in the right lobe) and 19 had multiple abscesses. In those who had multiple abscesses, they were confined to one lobe in 7 patients (unilobar multiple abscesses, Fig. 1); the remaining 12 had bilobar abscesses.

Abscess cultures were positive in 80% of patients and blood cultures were positive in 46%, rates consistent with those reported in other series.[6-8,11-15] The majority (17 of 28) of isolates were monomicrobial. The specific organisms isolated (Table III) were most commonly facultative gram-negative rods, especially *Escherichia coli* and *Klebsiella* spp. Gram-positive aerobes were isolated from 11 abscesses; *Streptoccoccus faecalis* was the predominant species (5 of 11). Fungi (*Candida* or *Aspergillus*) were recovered from the abscesses of three patients.

Deaths

The overall death rate in our series was 23%; when patients in whom the diagnosis was made at autopsy were excluded, the rate was 14%. In all patients who died, including those whose liver abscesses were diagnosed at autopsy, death was primarily attributed to liver abscess or associated septicemia, or both. Because increasing age and number of abscesses have been associated with increased mortality,[1,11,12,16-18] the influence of these factors on all patients and on treated patients (n = 36) was assessed. The death rate was increased in patients over the of age 60 years compared with those

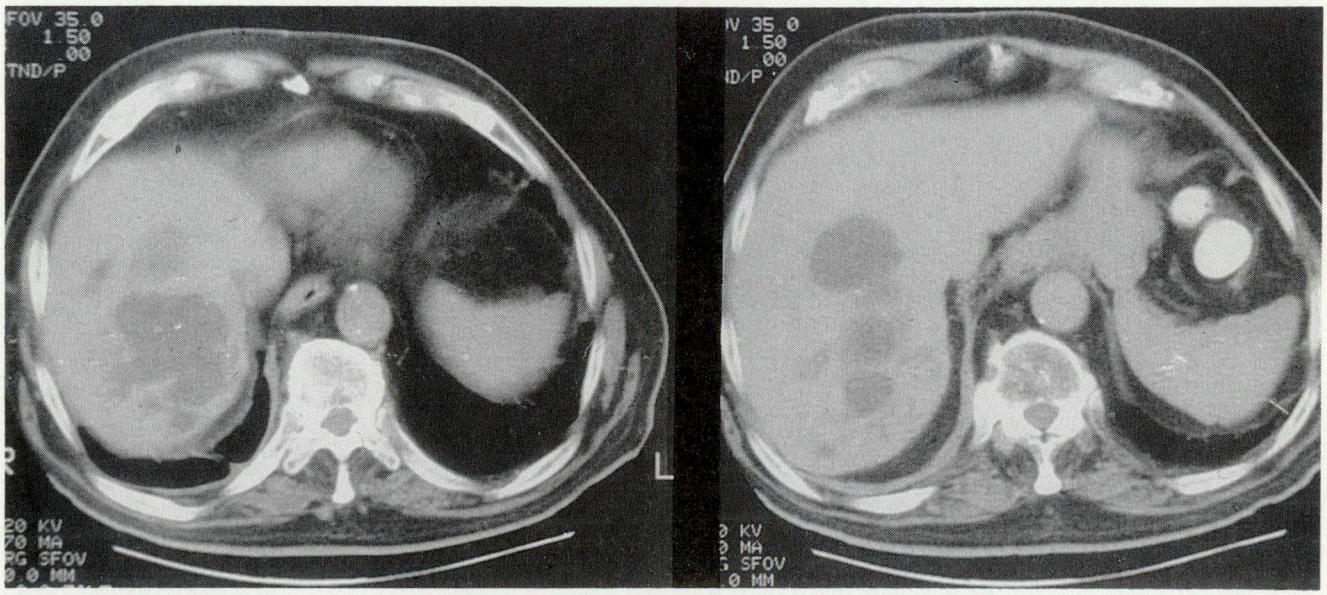

FIG. 1. Computed tomography scan demonstrating multiple pyogenic abscesses in right hepatic lobe.

under 60 (33% versus 11%). However, the four untreated patients (diagnosis made at autopsy) were all over 60 years old. When treated patients alone were analysed, the difference in death rate was reduced, being 18% and 11% in the over- and under-60 groups, respectively. Similarly, the overall death rate was greater in those with multiple abscesses (32%) than in those with single (14%) abscessès, when the entire patient population was considered. Once again, however, the four untreated patients had multiple abscesses, and when they were eliminated from the analysis, the death rates were similar for those with single and with multiple abscesses (14% and 13%, respectively). The death rate did not differ in treated patients admitted to medical wards (7%, 1 of 15) and surgical wards (8%, 1 of 12), but was higher in patients admitted to the intensive care unit (33%, 3 of 9).

Treatment and Outcome

All of the 36 patients in our series who were treated for pyogenic liver abscess received broad-spectrum antimicrobial therapy and in all but 5, some type of drainage procedure was performed. Treatment success was defined as clinical and radiologic resolution of liver abscesses, followed by hospital discharge.

Five patients received intravenously administered antibiotics alone; in three blood cultures were positive, and in one abscess cultures were also positive. The latter was an immunosuppressed patient with disseminated candidiasis who experienced clinical and radiologic resolution of his liver abscess after

Table III. Microorganisms Recovered From Abscess and Blood Cultures*

	Monomicrobial		Polymicrobial		Totals	
Organisms	**Abscess**	**Blood**	**Abscess**	**Blood**	**Abscess**	**Blood**
Gram-negative aerobes						
Escherichia coli	4	2	3	2	7	4
Klebsiella spp	3	3	4	3	7	6
Proteus mirabilis			1	1	1	1
Morganella morganii			1	1	1	1
Citrobacter aerogenes			2		2	
Acinetobacter sp	1				1	
Pseudomonas aeruginosa			1		1	
Eikenella corrodens			1		1	
Haemophilus influenzae			1		1	
Totals	8	5	14	7	22	12
Gram-positive aerobes						
Streptococcus faecalis		1	5	2	5	3
Streptococcus viridans			2	1	2	1
Streptococcus pyogenes		1	1		1	1
Streptococcus bovis		1	1		1	1
Staphylococcus aureus	1		1		2	
Totals	1	3	10	3	11	5
Gram-negative anaerobes						
Bacteroides fragilis		1	2		2	1
Bacteroides sp	1	1			1	1
Eubacterium sp				1		1
Fusobacterium nucleatum	1				1	
Totals	2	2	2	1	4	3
Gram-positive anaerobes						
Microaerophilic *Streptococcus*	5	1	1	1	6	2
Peptostreptococcus	1		1		2	
Clostridium perfringens			1		1	
Totals	6	1	3	1	9	2
Fungi						
Aspergillus	1				1	
Candida	1	1	1	1	2	2
Totals	2	1	1	1	3	2

*Figures are the number of patients from whom a particular microorganism was isolated.

intravenous amphotericin therapy. In one man a diagnosis of chronic cholecystitis was made 2 weeks after he had undergone cholecystectomy, and a swab of the gallbladder was positive for *E. coli* and *Klebsiella*. A 12 × 8 cm right intrahepatic abscess developed from which pus was aspirated, but a drainage catheter was not left in. He improved with broad-spectrum antibiotic therapy and his abscess eventually resolved. A third patient presented with a 12-month history of low-grade fever and was found to have a 7 × 6 cm abscess in the right lobe which was aspirated; no drain was left in. She, too, improved on broad-spectrum intravenous antibiotic therapy. Those three patients were treated on medical wards, and the surgical service was not consulted. Two patients refused drainage: in one, the diagnosis of liver abscess was made after a long course of antibiotic treatment during which the patient improved clinically; he continued to improve and his abscess resolved. The other patient who refused drainage was an 87-year-old woman with cholangitis who subsequently died of septic shock. The overall success rate for medical treatment alone was therefore 80% (4 of 5) with a death rate of 20% (Table IV). It is noteworthy that two of the survivors had a single percutaneous aspiration of their abscesses.

Comparison of PCD and OD

Demographic characteristics of patients initially treated with PCD were compared with those of patients initially treated with OD (Table V). The patients in each group were comparable with respect to age and duration of symptoms before treatment. The chief demographic difference between patients treated with PCD and those treated with OD was in the year of admission. The majority of patients treated with PCD were admitted between 1985 and 1987 (11 of 16) whereas most of the patients who underwent surgical drainage (10 of 15) were admitted between 1982 and 1984. It was difficult to determine what the rationale for the chosen mode of treatment had been. There was a trend toward treating patients who had recently undergone laparotomy (within 6 months) with OD (five of seven patients). Of the five patients treated by OD between 1985 and 1987, the diagnosis was made at laparotomy in three, one had recently undergone laparotomy and one had a post-traumatic liver abscess.

Outcome parameters including treatment success, death and complication rates, and duration of hospital stay, were compared in patients managed with PCD and OD. Although the demographic characteristics of these two groups were similar, a statistical analysis of results was not considered appropriate, since entry into the two groups had been nonrandom. Sixteen patients underwent PCD as their initial therapy with a success rate of 75% (Table IV). Of the four patients in whom PCD failed, two died and two recovered after subsequent OD. Open drainage was the initial procedure in 15 patients, with a success rate of 87%; the 2 patients in whom OD failed died of sepsis and multiple organ failure.

Since multiplicity of abscesses has been considered a predictor of poor outcome,[1,11,12,16-18] we analysed the success rates of PCD and OD in cases of single and multiple abscesses. Single abscesses were well treated by either modality, with success rates of 86% with PCD versus 90% with OD. For patients with multiple abscesses, OD appeared at first glance to be a superior mode of therapy with a success rate of 80% compared with the PCD rate of 67%. However, when the patients

Table IV. Treatment and Outcome

Treatment	No.	Success, no. (%)	Death, no. (%)
Antibiotics alone	5	4 (80)	1 (20)
Antibiotics and PCD	16	12 (75)	2 (13)
Antibiotics and OD			
Initial	15	13 (87)	2 (13)
After failure of PCD	2	2 (100)	0
Totals	17	15 (88)	2 (12)

PCD = percutaneous drainage, OD = operative drainage.

Table V. Comparison of Patient Characteristics: Percutaneous Drainage (PCD) Versus Operative Drainage (OD)

Characteristic	PCD	OD
No. of patients	16	15
Age, yr		
Range	20 – 87	20 – 91
Median	56	59
Sex, M:F	13:3	9:6
Median duration of symptoms, d	8.5	11
Year of admission		
1982 – 1984	5	10
1985 – 1987	11	5

with multiple abscesses were subdivided into those with unilobar and those with bilobar multiple abscesses, an interesting difference in outcome emerged. Patients with unilobar multiple abscesses achieved 100% treatment success whether treated with PCD or with OD; those treated with PCD (four patients) were all managed with a single catheter only (Fig. 2). Overall success rates were much lower for bilobar multiple abscesses, although higher for OD (67%) than for PCD (40%). In only two of the five patients with bilobar multiple abscesses was treatment with PCD successful. In these two patients, multiple drainage catheters were required to achieve satisfactory drainage. In contrast, only a single catheter had been used for the three patients in whom PCD failed. Failure to employ multiple drainage catheters in these three patients may have been responsible for treatment failure.

Complication rates were similar for PCD (2 of 16, 13%) and OD (3 of 15, 20%). In one patient peritoneal signs developed the day after PCD, and OD was performed to drain both the liver abscess and the contaminated peritoneal cavity; the patient's recovery was uncomplicated. Another patient suffered a hemothorax after percutaneous catheter insertion; this was adequately treated by insertion of a chest tube. Of the three patients who experienced complications after OD, one had serious intraoperative hemorrhage from the liver which required packing and repeat laparotomy, which was followed by a successful recovery. A second patient had multiple pulmonary emboli and required heparinization. The third patient suffered an upper gastrointestinal hemorrhage and followed a progressive course of sepsis, multiple organ failure and death.

Patients treated with PCD were assessed for resolution of abscesses using US or CT, or both, before drainage catheters are removed. Median duration of catheter drainage in these patients was 4 weeks. Typically, patients were discharged from hospital with the drainage catheter in place. Catheters were removed after abscess resolution had been confirmed by US, CT or sinography.

Some authors have reported a significantly prolonged hospital stay in patients who have undergone PCD compared with OD.[6,8] Indeed, those managed with OD had a shorter mean hospital stay (Table VI), both total and following the initiation of appropriate therapy (i.e., antibiotics and drainage). The difference was most marked in patients admitted to surgical wards. The mean duration of hospital stay following initiation of treatment was longest for patients treated with antibiotics alone (34 days).

Discussion

Although pyogenic liver abscess is not a frequent diagnosis (ranging from 9 to 15 per 100 000 hospital admissions[8,11,12]), the high death rate when it is left untreated[12,18–20] makes it an important clinical entity. The impact of early diagnosis on outcome in pyogenic liver abscess is illustrated by the marked decline in death rates since the advent of readily available US and CT (accompanied by prompt drainage) in the early 1980s.[7,9,10,18] This appears in part to be related to an increased antemortem diagnosis rate. Of the 40 patients in the present series, the diagnosis made at autopsy in only 4, and they were seen during the early part of the review period (1982 and 1983). In contrast, before the introduction of high-resolution imaging techniques, only 50% to 70% of liver abscesses were diag-

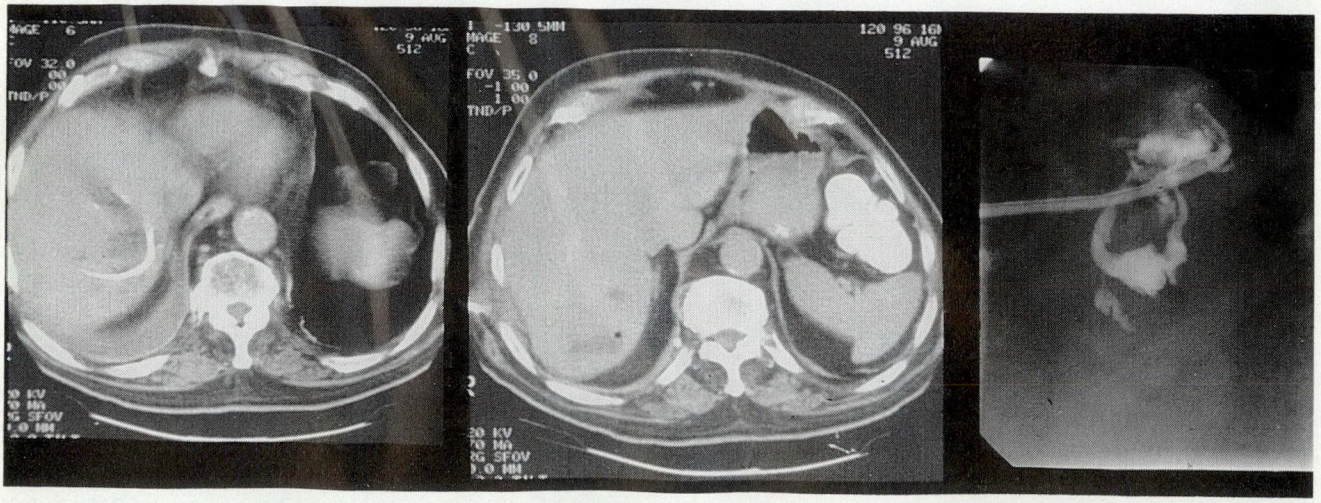

FIG. 2. Follow-up scan and sinogram 1 week after institution of percutaneous catheter drainage demonstrate resolving abscess cavities. Interconnections between cavities can be seen in sinogram.

nosed ante mortem.[12,19-21] Similarly, early diagnosis and highly accurate localization have probably contributed to improved outcome in our own and other recent series.

Ultrasonography and CT should probably be viewed as complementary modalities in the investigation of suspected liver abscess. Their reported sensitivity rates are comparable but, as in this series, are slightly higher for CT (95% to 100%)[7,11,12,22,23] than for US (80% to 90%).[7,10,11,12] Although US has the advantage of being noninvasive and mobile, its usefulness can be limited by obesity, excess gastric or colonic gas, interoperator variability and the difficulty in detecting small abscesses located near the hemidiaphragm.[7,9] Computed tomography is superior in detecting abscesses in this location. Both modalities are also useful in assessing the results of therapy; in our patients, collapse of the abscess cavity as judged by US and CT was used as one of the criteria for removing drainage catheters.

Follow-up imaging is crucial to ensure that the original abscess cavities have been drained and to investigate for the development of new abscesses or the presence of previously unrecognized collections. Frey and colleagues[9,24] emphasized that failure to drain one of several abscesses was as lethal as not draining a solitary abscess. Such failure has likely been responsible for the higher death rates traditionally reported for multiple abscesses. This point is illustrated by the five patients in this series with bilobar multiple abscesses treated by PCD: the two in whom PCD was successful were treated with multiple (three and four) drainage catheters, and the three in whom PCD failed were treated with a single catheter only.

In contrast to the requirement for multiple catheters for bilobar abscesses, all four patients with unilobar "multiple" abscesses treated by PCD had resolution of the abscesses with insertion of a single drainage catheter only. This result supports the notion that such unilobar "multiple" abscesses are usually multiloculated single abscesses with free communication between the locules[25] (Fig. 2). Effective drainage can therefore be achieved with a single drain, whether inserted percutaneously or at laparotomy. With treatment of multiple abscesses based upon the above principles, Farges, Leese and Bismuth[10] reported a comparable prognosis for patients with multiple and solitary hepatic abscesses. Similarly, in our series, the death rates were comparable in treated patients who had solitary (14%) and multiple (13%) abscesses.

The overall success rate in patients treated with antibiotics and drainage (either PCD or OD) in the present series was 87% (27 of 31). The success and complication rates for PCD (75% and 13%, respectively) were comparable to those for OD (87% and 20%) and approximate those achieved with PCD in other recent series (success in 65% to 90%,[6-8,10,25,26] complications in 4% to 20%.[7,10,25,27-29] With equivalent overall results using either PCD or OD, other factors require consideration in formulating the relative roles of PCD and OD in the optimal management of pyogenic liver abscesses. Clinical scenarios favouring OD include: (a) the need for additional concomitant surgery (e.g., drainage of the biliary tree), (b) the inability to drain the infection percutaneously due to the presence of infected necrotic tissue rather than pus and (c) failure of PCD. Failure of PCD to achieve clinical improvement within 24 hours should be an indication for radiologic reassessment. If additional abscesses have developed, these should be drained promptly.

In their review of 33 cases of pyogenic liver abscess seen between 1979 and 1985, Klatchko and Schwartz[8] concluded that operative drainage should remain the primary mode of treatment. This conclusion was based on the high rate of treatment failures (6 of 11) in patients initially managed with PCD. However, PCD was used as a secondary treatment in 6 patients, with success in all, so that of a total of 17 PCD drainage procedures, 11 were successful. This compares with a failure rate of 33% (6 of 18) in those patients initially treated with operative drainage, and a total of 20 operative drainage procedures, 14 of which were successful.

One major objection raised against PCD is that it prolongs hospital stay. Bertel, van Heerden and Sheedy[6] reported that in patients treated with PCD the mean duration of hospital stay was 37 days compared with 26 days for those treated operatively. More recently, Attar, Levendoglu and Cuassay[26] reported a mean stay of 21 days in 15 patients treated with

Table VI. Length of Hospitalization (Mean + SEM) in Surviving Patients

Hospitalization	PCD, d (no.)	OD, d (no.)
Total stay	35 ± 6 (14)	27 ± 4 (13)
Following initial therapy		
Overall	29 ± 4 (14)	22 ± 3 (13)
Patient location:		
ICU then surgical ward	42 ± 5 (4)	38 ± 5 (2)
Medical ward	22 ± 6 (6)	29 ± 3 (4)
Surgical ward	30 ± 8 (4)	12 ± 2 (7)

PCD = percutaneous drainage, OD = operative drainage, ICU = intensive care unit.

PCD. In our own series, both total stay and stay after the initial drainage procedure were approximately 1 week longer for PCD than OD patients. The reason for this discrepancy is not understood. In our series, however, it did not relate to the clinical service on which the patient was treated. Another possibility may be the severity of illness when treatment is initiated. We are currently undertaking a prospective study of patients with the diagnosis of pyogenic liver abscess which will include determination of APACHE II scores before therapy. This may assist in determining whether severity of underlying illness or mode of drainage is a more important determinant of length of stay. Stratification according to severity of illness may also provide information which will help optimize the selection of therapy for an individual patient.

Conclusions and Recommendations

The clinical presentation of pyogenic liver abscess, including laboratory findings, is nonspecific. Any suspicion of the diagnosis warrants early radiologic investigation.

Both CT and US are sensitive modalities in the diagnosis of liver abscesses. Should US fail to detect an abscess where it is clinically suspected, CT should be done. One or both of these modalities should be used to assess adequacy of abscess drainage.

Percutaneous drainage and operative drainage appear to be equally efficacious in the treatment of solitary pyogenic liver abscesses and unilobar multiple abscesses.

Bilobar multiple abscesses are more difficult to manage and carry a correspondingly higher death rate than that for single or unilobar multiple abscesses. Bilobar multiple abscesses can probably be successfully managed by either OD or PCD, as long as multiple drainage catheters are used in the latter case. Follow-up imaging should be done frequently to rule out the presence of undrained or newly evolved abscess cavities.

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When choosing an antibiotic for nosocomial infections,

LOOK BEYOND THE PRICE TAG.

Look at the safety profile and total cost of treatment.

Significant biliary excretion of antibiotics can have a very disruptive effect on intestinal flora, which may promote the emergence of resistant strains of bacteria and cause diarrhea.[1,2] This can add substantially to the cost of treatment.[3]

CLAFORAN (cefotaxime sodium) has an excellent safety profile. With only 5% biliary excretion, Claforan has little effect on intestinal flora, thus reducing the risk of diarrhea and bacterial resistance.[1,4] And Claforan provides excellent coverage of major nosocomial pathogens.

Over a complete course of therapy, if one looks at the average cost per patient, Claforan makes good sense.[5]

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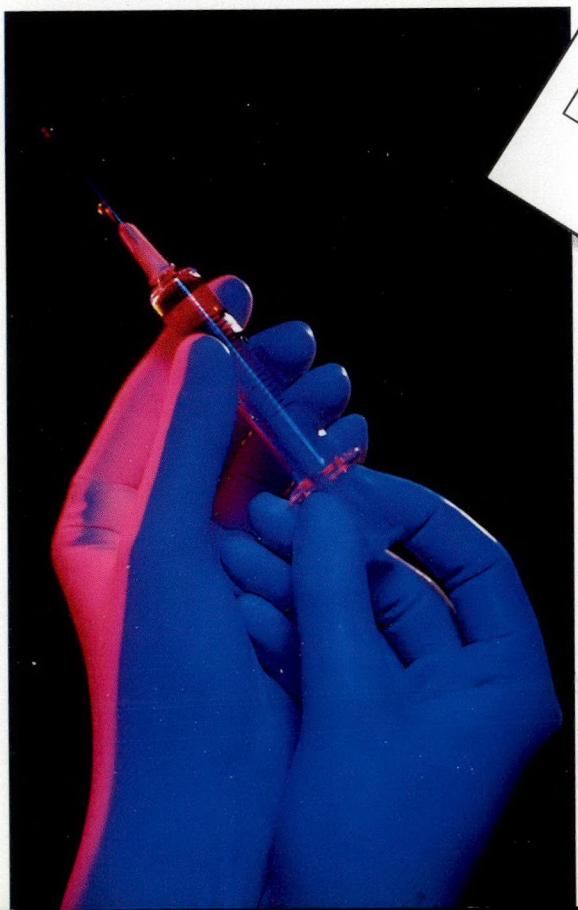

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Action

In vitro studies indicate that the bacterial action of Claforan (cefotaxime sodium) a semi-synthetic cephalosporin antibiotic, results from inhibition of cell wall synthesis.

Indications and Clinical Uses

Treatment : Claforan (cefotaxime sodium) may be indicated for the treatment of infections caused by susceptible strains of the designated micro-organisms in the diseases listed below.

Lower respiratory tract infections : pneumonia and lung abscess caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), other streptococci (excluding enterocci, e.g. *S. faecalis*), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli*, *Hemophilus influenzae*, (including ampicillin resistant strains) and unspecified *Klebsiella* species.

Urinary tract infections : caused by *Escherichia coli*, unspecified *Klebsiella* species (including *K. pneumoniae*), *Proteus mirabilis*, indole positive *Proteus*, *Serratia marcescens* and *Staphylococcus epidermidis*. Also, uncomplicated gonorrhea caused by *N. gonorrhoeae* including penicillin resistant strains.

Bacteremia / Septicemia : caused by *Escherichia coli*, unspecified *Klebsiella* strains and *Serratia marcescens*.

Skin infections : caused by *Staphylococcus aureus* (penicillinase and non-penicillinase producing, *S. epidermidis*, Group A streptococci, *Escherichia coli*, *Proteus mirabilis* and indole positive *Proteus*.

Intra-abdominal infections : caused by *Escherichia coli*, and unspecified *Klebsiella* species.

Gynecological infections : including pelvic inflammatory disease, endometritis and pelvic cellulitis caused by *E. coli*, Group A streptococci and *Staphylococcus epidermidis*; anaerobic bacteria including unspecified *Peptococcus* and *Peptostreptococcus* strains and some strains of *Bacteroides fragilis*. In several cases, although clinical cures were achieved, bacteriological follow-up was not available.

Central nervous system infections : meningitis and ventriculitis caused by *Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Escherichia coli*. Claforan is not active against *Listeria monocytogenes*.

Clinical experience with Claforan in anaerobic infections is limited. Claforan has been used with some success in wound and intra-abdominal infections against some strains of unidentified *Bacteroides* and anaerobic cocci.

Claforan has been shown to be active against some strains of *Pseudomonas*.

In the treatment of infections encountered in immunosuppressed and granulocytopenic patients, results of therapy with Claforan have not been impressive.

Claforan should not be considered in the treatment of enterococcal infections, i.e. *Streptococcus faecalis*.

Specimens for bacteriologic culture should be obtained prior to therapy in order to isolate and identify the causative organisms and to determine their susceptibilities to Claforan. Therapy may be instituted before results of susceptibility studies are known; antibiotic treatment should be re-evaluated once these results become available.

Prophylactic Use : The administration of Claforan perioperatively (preoperatively, intraoperatively and postoperatively) may reduce the incidence of certain infections in patients undergoing elective surgical procedures (e.g. abdominal or vaginal hysterectomy, gastrointestinal and genitourinary tract surgery) that may be classified as contaminated or potentially contaminated.

In patients undergoing caesarian section who are considered to be at increased risk of infection, intraoperative (after clamping the umbilical cord) and postoperative use of Claforan may also reduce the incidence of certain postoperative infections.

Effective use for elective surgery depends on the time of administration (see Dosage and Administration).

For patients undergoing gastrointestinal surgery, preoperative bowel preparation by mechanical cleansing as well as with a non-absorbable antibiotic (e.g. neomycin) is recommended.

If there are signs of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapy may be instituted.

Contraindications

Claforan is contraindicated in patients who have shown hypersensitivity to cefotaxime sodium, the cephalosporin or the penicillin groups of antibiotics.

Warnings

Before therapy with Claforan is instituted, it must be carefully determined whether the patient has had previous hypersensitivity reactions to cefotaxime, cephalosporins, penicillins or other drugs. Claforan should be given with caution to patients with Type 1 hypersensitivity reactions to penicillin. Antibiotics, including Claforan should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to Claforan occurs, the drug should be discontinued and the patient treated with the usual agents (e.g. epinephrine, antihistamine, pressor-amines or corticosteroids).

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea during the administration of Claforan. This colitis can range from mild to life-threatening in severity.

Treatment with broad spectrum antibiotics, such as Claforan, alters the normal flora of the colon and may permit overgrowth of *Clostridium difficile* or other clostridia. It has been established that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of colitis may respond to discontinuation of Claforan and replacement with a suitable specific antibiotic. Moderate to severe cases should be managed with fluid, electrolyte and protein supplemntation as indicated.

When the colitis is not relieved by discontinuance of Claforan administration or when it is severe, an antibiotic specifically effective in antibiotic-associated pseudomembranous colitis (e.g. vancomycin) or other suitable therapy may be indicated. Other possible causes of colitis should also be considered (see Adverse Reactions).

Precautions

Claforan (cefotaxime sodium) should be prescribed with cauton in individuals with a history of lower gastro-intestinal disease, particularly colitis.

The safety of Claforan in pregnancy has not been established. Consequently, use of the drug in pregnant women requires that the likely benefit from the drug be weighed against the possible risk to the mother and fetus.

Use of Claforan in women of child-bearing potential requires that the anticipated benefits be weighed against the possible risks.

Cefotaxime is excreted in human milk in low concentrations. Caution should be exercised when the drug is administered to nursing mothers.

Prolonged use of Claforan may result in the overgrowth of nonsusceptible organisms. Constant evaluation of the patient's condition is essential. If super-infection occurs, therapy should be discontinued and appropriate measures taken.

Although Claforan rarely produces alterations in kidney function, evaluation of renal status is recommended, especially in severely ill patients receiving high doses.

Patients with markedly impaired renal function should be placed on the special dosage schedule recommended under Dosage and Administration, because normal dosage in these individuals is likely to produce excessive and prolonged serum antibiotic concentrations.

Positive direct Coomb's test is known to develop in individuals during treatment with the cephalosporin group of antibiotics, including cefotaxime sodium.

In laboratory tests a falso positive reaction to glucose may occur with reducing substances but not with the use of specific glucose oxidase methods.

Adverse Reactions

The most frequent adverse reactions with their frequency of occurrence are :

Hypersensitivity (1.8%) : Rash, pruritus, fever. Local (5%) : Injection site inflammation with intravenous administration. Pain, induration and tenderness after intramuscular injection. Gastrointestinal (1.7%) : Colitis, diarrhea, nausea and vomiting. Symptoms of pseudomembranous colitis can appear during or after Claforan treatment. Hemic and Lymphatic System (< 1%) : Mild, reversible leukopenia, granulocytopenia and thrombo-cytopenia have been reported. Some patients developed positive direct Coomb's test during treatment with Claforan. Genitourinary System (< 1%) : Moniliasis, vaginitis. Liver (< 1%) : Transient elevations in SGOT, SGPT, serum LDH and serum alkaline phsphatase levels have been reported. Kidney (< 1%) : Increased serum creatinine and BUN have occasionally been observed. Central Nervous System (0.2%) : Headache.

Symptoms and Treatment of Overdosage

Since no case of overdosage has been reported to date with Claforan, no specific information on symptoms or treatment is available. Treatment of overdosage should be symptomatic.

Dosage and Administration

Claforan (cefotaxime sodium) may be administered intramuscularly or intravenously after reconstitution (see Table with recommended mode of reconstitution according to route of administration).

Adults

The dosage of Claforan should be determined by susceptibility of the causative organisms, severity of the infection and condition of the patient.

Guidelines for Dosage of Claforan (cefotaxime sodium)

Type of Infection	Daily Dose (g)	Frequency and Route
Uncomplicated Gonorrhea	1	1 g IM (single dose)
Uncomplicated infections	2	1 g every 12 hours IM or IV
Moderately severe to severe infections	3-6	1-2 g every 8 hours IM or IV
Very severe infections (e.g. septicemia, CNS)	6-8	2 g every 6-8 hours IV
Life-threatening infections	up to 12	2 g every 4 hours IV

To prevent postoperative infection in contaminated or potentially contaminated surgery, recommended doses are as follows.

(a) 1 g IM or IV administered 1/2 to 1-1/2 hours prior to the initial surgical incision to ensure that adequate antibiotic levels are present in the serum and tissues at the start of surgery

(b) 1 g IM or IV administered 1-1/2 to 2 hours following the first dose; for lengthy operative procedures, additional intraoperative doses may be administered, if necessary, at appropriate intervals (1-1/2 to 2 hours) during surgery

(c) 1 g IM or IV administered within 2 hours following completion of surgery

The total cumulative prophylactic dose should not exceed 6 g in a 12 hour period.

Caesarian Section Patients

The first dose of 1 g is administered IV as soon as the umbilical cord is clamped. The second and third doses should be given as 1 g IM or IV at 6 and 12 hours after the first dose.

Neonates, Infants, and Children

The following dosage schedule is recommended :

Neonates : 0-1 week of age — 50 mg / kg IV q 12 h
1-4 weeks of age — 50 mg / kg IV q 8 h

Infants and children (1 month to 12 years) : For body weights less than 50 kg, the recommended daily dose is 50 to 100 mg / kg IM or IV of body weight divided into 4 to 6 equal doses, or up to 180 mg / kg / day for severe infections (including central nervous system infections).

For body weights 50 kg or more, the usual adult dosage should be used.

The maximum daily dosage should not exceed 12 grams.

Administration of Claforan should be continued for a minimum of 48 to 72 hours after the patient defervesces or after evidence of bacterial eradication has been obtained; a minimum of 10 days of treatment is recommended for infections caused by Group A beta-hemolytic streptococci in order to guard against the risk of rheumatic fever or glomerulonephritis; frequent bacteriologic and clinical appraisal is necessary during therapy of chronic urinary tract infections and may be required for several months after therapy has been completed; persistent infections may require prolonged treatment. Doses less than those recommended should not be employed.

Dosage for Patients with Impaired Renal Function

In patients with estimated creatinine clearance of less than 20 mL / min / 1.73m^2 the dose of Claforan should be halved (see Precautions).

If serum creatinine values alone are available, the following formula (based on sex, weight, and age of the patient) may be used to convert these values into creatinine clearance.

Males : $\dfrac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine}}$

Females : 0.85 × above value

Administration

Intramuscular : Claforan should be injected well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e. gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel.

Intravenous : The intravenous route is preferable for patients with bacteremia, bacterial spticemia, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.

For bolus administration a solution containing 1 or 2 g of Claforan can be injected over a period of 3 to 5 minutes. Using an infusion system, it may also be given over a longer period of time through the tubing system by which the patient may be receiving other intravenous solutions. Butterfly* or scalp vein type needles are preferred for this type of infusion. However, during infusion of the solution containing Claforan, it is advisable to discontinue temporarily the administration of other solutions at the same site.

ADD-Vantage* Vial

When administering Claforan using the ADD-Vantage* Drug Delivery system, Claforan powder is added directly to a single-dose flexible plastic ADD-Vantage* diluent container. Claforan 1 g or 2 g may be reconstituted in 50 mL or 100 mL of 5% Dextrose Injection USP or 0.9% Sodium Chloride Injection USP.

Stability

Solutions of Claforan reconstituted in 5% Dextrose Injection USP or 0.9% Sodium Chloride Injection USP in the ADD-Vantage* flexible containers maintain satisfactory potency for 12 hours at room temperature.

Availability

Claforan (cefotaxime sodium) is supplied as a sterile, white to pale yellow powder, in vials containing 500 mg, 1.0 and 2.0 g of cefotaxime sodium and in ADD-Vantage* vials containing 1.0 and 2.0 g of cefotaxime sodium (expressed as acid on a dry basis).

Storage : Claforan in the dry state should be stored at room temperature protected from light and heat.

Product monograph available on request.

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Ex-Vivo Microvascular Reconstruction Before Renal Allograft and Autograft Transplantation

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Microvascular reconstruction was performed ex vivo on 50 kidneys that had vascular anomalies or had sustained vascular injury during procurement before allograft transplantation or autotransplantation. The authors review the various surgical techniques used to facilitate the in-situ vascular anastomoses during transplantation and to salvage otherwise an unusable allograft. The complications associated with the microvascular repair were negligible. The authors conclude from the results of their study that ex-vivo microvascular reconstruction is a valuable adjunct to renal transplantation.

Une microreconstruction vasculaire a été pratiquée ex-vivo sur 50 reins qui présentaient des anomalies vasculaires ou qui avaient subi des lésions vasculaires au cours du prélèvement en vue d'une allogreffe ou d'une autogreffe. Les auteurs passent en revue les diverses techniques chirurgicales utilisées pour faciliter une anastomose vasculaire in situ, durant la transplantation, et pour préserver une allogreffe qui serait, autrement, inutilisable. Les complications reliées à la microchirurgie vasculaire sont négligeables. Les auteurs concluent des résultats de leur étude que la microreconstruction vasculaire ex-vivo est un appoint thérapeutique utile à la transplantation rénale.

Microvascular bench surgery was used to reconstruct the vasculature of 50 kidneys before renal allograft transplantation. All kidneys had vascular anomalies (including a renal artery aneurysm) or vascular injury sustained during procurement. The purpose of the repair was to facilitate the in-situ vascular anastomosis in the recipient or to salvage an otherwise "unusable" allograft. Although utilization of the Carrel patch is the procedure of choice for donor kidneys with multiple vessels, its use is sometimes precluded (e.g., in live donors, when kidneys are harvested without an aortic patch or when the arteries have remote aortic origins). The value of adjunctive microvascular reconstruction is also illustrated in this paper.

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Patients and Methods

Between January 1985 and June 1989, 35 cadaveric kidneys and 13 kidneys from living-related donors were repaired and transplanted into 48 patients with end-stage renal failure. Two patients underwent renal autotransplantation after ex-vivo microvascular repair. The kidneys from cadaveric donors were harvested en bloc with in-situ perfusion whenever possible. Vascular repair was performed in a basin of iced saline. Optical magnification was provided by either the Zeiss operating microscope (10× magnification) or optical loupes (2.5× magnification), depending on vessel size. Standard microsurgical instruments and monofilament nonabsorbable 8-0, 9-0 or 10-0 sutures were used.

Surgical Technique

Multiple Vessels

Two basic microvascular anastomoses were used, either alone or in combination, depending on the vascular problem of each kidney. Vessels of comparable calibre were anastomosed side to side with running suture to create a single ostium from the two vessels (Fig. 1). Small polar vessels were anastomosed end to side to the main artery with interrupted sutures after

excision of a patch of vessel wall sufficient to accommodate the small vessel (Fig. 2). A small, plastic intravenous cannula was used as an intraluminal stent, safeguarding against injury to the posterior wall of the vessel during the anastomosis.

Vascular Injury

When the vessels had been injured during procurement and the kidneys were otherwise usable, individual vascular reconstruction was performed. An end-to-end anastomosis with interrupted sutures was feasible when the vessels had been cleanly severed without loss of length. If a substantial length of the vessel had been lost (usually from an unsuspected polar branch), the polar vessel was anastomosed end to side to the main artery at a new site near the renal hilum, providing a tension-free anastomosis. In two kidneys with extensive vascular injury harvested at a non-transplant centre a combination of the techniques was used. The end-to-end technique was used in two other kidneys with a severed polar vessel.

Short Renal Vein

Kidneys having a very short renal vein were reconstructed by incorporating the proximal inferior vena cava as part of the renal vein in a manner previously described[1] (Fig. 3). Usually a 7-0 nonabsorbable monofilament running suture was used. The renal vein length was increased two- to threefold in all cases.

Renal Artery Aneurysm

The renal arteriogram on a live donor revealed a solitary renal artery bilaterally. When the kidney was harvested, a renal artery aneurysm, 1.6 cm in diameter, was discovered at the bifurcation of the main artery and a lower pole branch. Standard donor nephrectomy was completed and microvascular repair performed before transplantation into the recipient. The aneurysm was excised and the detached lower pole vessel was anastomosed end to side to the ostium of the aneurysm after appropriate spatulation.

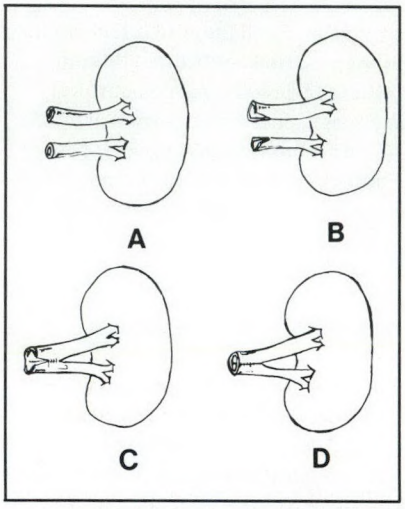

FIG. 1. Vessels of comparable calibre were anastomosed side to side with running suture to create single ostium. Note splitting of arterial wall in B.

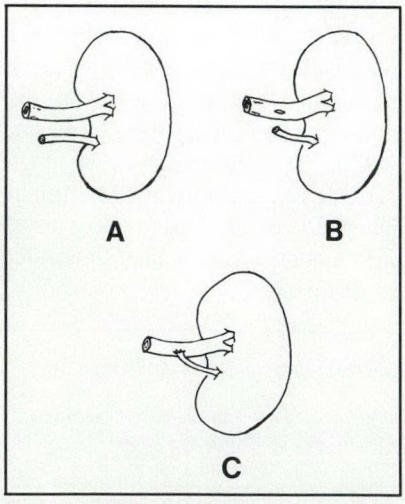

FIG. 2. Small polar vessel was anastomosed end to side to main artery with interrupted sutures after creating arteriotomy on main vessel.

Renal Autotransplantation

One patient had a long impassable ureteral stricture secondary to previous ureteroscopic instrumenta-

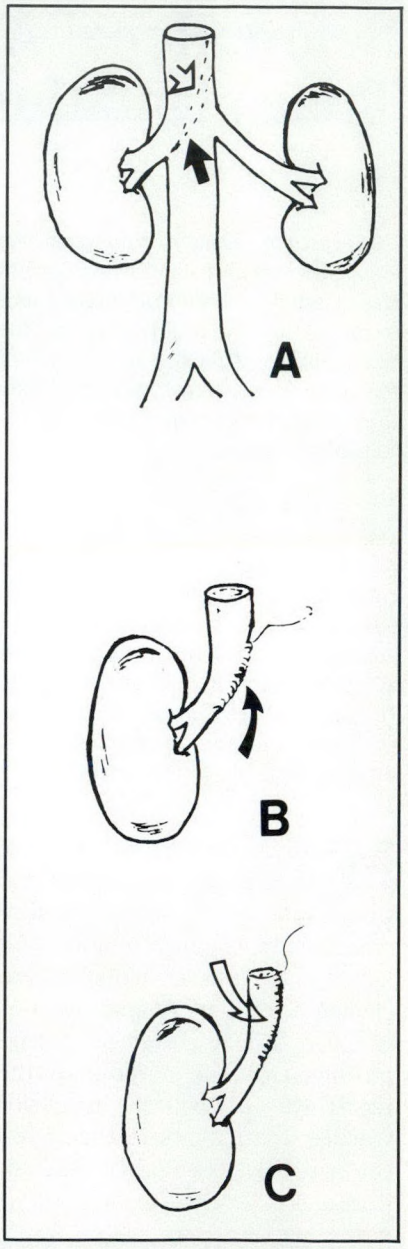

FIG. 3. Short right renal vein was elongated by incorporating inferior vena cava. Cava is incised obliquely either along line indicated by solid arrows in A with reconstruction illustrated in B or along line indicated by open arrow in A with reconstruction illustrated in C. Running 7-0 nonabsorbable monofilament suture is used.

tion. Autotransplantion was undertaken to salvage the obstructed kidney, which had an accessory artery at its lower pole. Standard end-to-side microanastomosis was performed (lower pole to main artery) and the graft was autotransplanted with a single in-situ arterial and venous anastomosis. The second patient had a centrally located renal cell carcinoma in a solitary kidney. The carcinoma measured 5 cm in diameter and directly abutted on the renal pelvis. The renal arteriogram suggested a very early anterior branch supplying the tumour (Fig. 4). On the assumption that it supplied the tumour primarily, the branch was identified intraoperatively, ligated and divided before the standard radical nephrectomy was carried out. The tumour was excised ex vivo with adequate margins of normal renal tissue, confirmed by random frozen-section examinations. The collecting system was repaired and the arterioles and venules, which were identified by indigo carmine infusion through the main renal artery and vein, were sutured. Infusion of indigo carmine through the previously severed end of the anterior arterial branch revealed that the branch supplied much more normal parenchyma in the middle zone of the kidney than anticipated. To minimize the risk of fistula and renal ischemia, the divided vessel was anastomosed end to end with interrupted 8-0 sutures. Standard autotransplantion into the right iliac fossa was performed after closure of the renal tumour bed (Fig. 4).

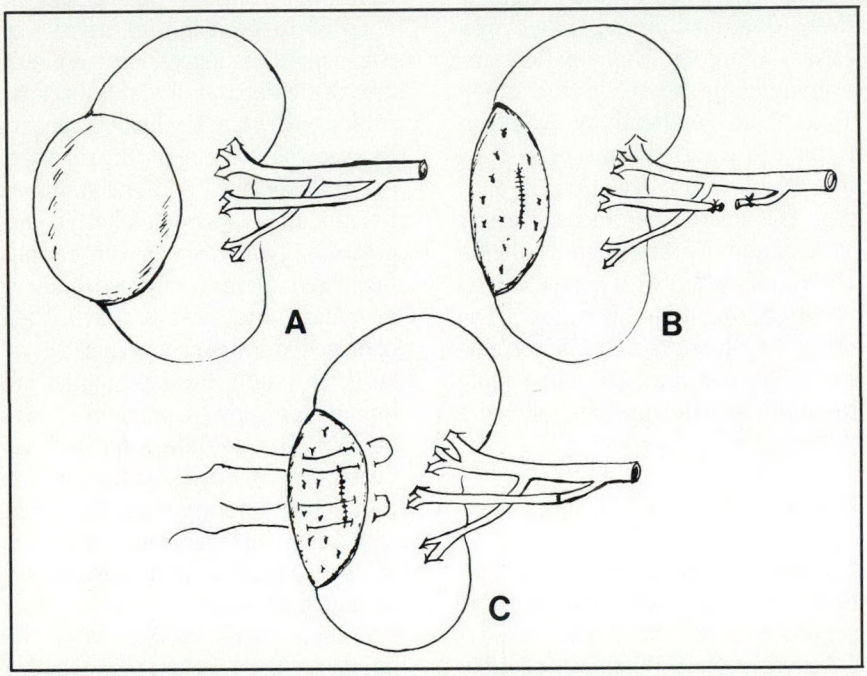

FIG. 4. (A) Renal cell carcinoma in solitary kidney. (B) Mid-pole branch ligated and divided and tumour excised ex vivo. Renal pelvis was closed. (C) Artery was reanastomosed end to end with interrupted 8-0 sutures after determining extent of blood supply by arterial branch. Tumour bed was closed with interrupted matress sutures.

Table I. Patient Data

Anatomic arrangement	Type of anastomosis	No. of grafts
Allografts		
Single anastomosis		
Polar artery	End to side	20
Duplicated arteries	Conjoint arteries	11
Duplicated veins	Conjoint veins	1
Short renal vein	Caval extension	4
Multiple anastomoses		
Duplicated arteries, veins	Conjoint arteries, veins	1
Polar artery, short vein	End-to-side artery; caval extension	1
Duplicated artery, short vein	Side-to-side artery; caval extension	1
3 arteries (2 main, 1 polar)	Polar end to side to main; 2 main side to side	2
3 arteries (2 main, 1 polar), duplicated veins	2 main on Carrel patch; polar end to side to main; conjoint veins	1
5 arteries	2 arteries both end to side to main; 2 small arterioles ligated	1
Damaged during procurement	Combination of end to side, side to side, end to end	4
Renal artery aneurysm	Excision of aneurysm; end to side, polar to main artery	1
Autografts		
Single anastomosis		
Polar artery	End to side	1
Early branch supplying tumour, middle zone	End to end	1

Results

Of the 48 patients who received allografts, 37 had a single anastomosis and 11 required multiple reconstructive procedures, including one aneurysm excision and repair (Table I). In both cases of autotransplantation, the patients required a single microanastomosis, end to side in one and end to end in the other. All reconstructed kidneys required a single arterial and venous anastomosis in situ. For the grafts with a short renal vein, the length

of the renal vein was routinely doubled or tripled by incorporating part of the vena cava, thus facilitating the in-situ exposure and anastomoses.

The average duration for the bench surgery was 35 minutes for a single arterial anastomosis, 15 minutes for a single venous reconstruction and 60 minutes for multiple procedures. The median warm ischemic (rewarm) time for the in-situ arterial and venous anastomoses was 27 minutes for the 45 transplants I performed. Three of the 45 grafts had a warm ischemic time exceeding 45 minutes because of technical problems unrelated to the microvascular reconstruction.

Two of the 50 reconstructed kidneys had a minor leak along the anastomotic suture line when the arterial clamp was released; one graft required a single hemostatic suture (8-0) at the leakage site, and in the other, bleeding was stopped with topical application of an absorbable Gelfoam pad. Satisfactory blood flow was observed through the reconstructed vessels with corresponding good parenchymal perfusion in all allografts and autografts as confirmed by nucleotide renal scanning 1 day postoperatively. There were no postoperative complications, such as hemorrhage or renal or ureteral devascularization, related to the microsurgery *per se*.

Nuclear scanning was repeated regularly only when indicated by persistent oliguria or anuria, a sudden rise in the serum creatinine level or a decline in urine output. Blood flow was uniform in all reconstructed kidneys and there were no detectable perfusion defects. In selected patients, renal arteriography was performed because of postoperative hypertension, an audible bruit over the area of the iliac vessels or declining renal function. One patient had stenosis at the allograft renal artery and host internal iliac artery anastomosis, remote from the end-to-end microanastomosis.

There were two deaths perioperatively, due to an intraoperative myocardial infarction in one patient and overwhelming sepsis in the other. Transplant nephrectomy was performed in three patients because of irreversible acute rejection; in each case the microanastomosed vessels were patent. Three patients suffered chronic rejection with a steady deterioration in renal function. The other 40 allografts and 2 autotransplants have maintained good renal function to date (median follow-up 26 months).

Discussion

Approximately 25% of donor kidneys have unilateral multiple renal vessels and 10% have bilateral vascular variations.[2] Whenever possible the Carrel aortic patch should be used to salvage such kidneys for transplantation. However, the use of the aortic patch is contraindicated in live donors, and the procedure is not technically feasible in some circumstances. Several macroscopic anastomotic techniques have been proposed to handle kidneys with multiple arteries,[3] although the techniques are cumbersome and in-situ exposure is usually suboptimal.

Microvascular reconstruction would greatly facilitate the in-situ vascular anastomoses, since excellent exposure and accurate anastomosis can be achieved with a minimum of technical errors. A conjoint "double-barrelled" artery has the theoretical hemodynamic advantage over two smaller vessels anastomosed individually to the recipient artery. Revascularization of multiple vessels in situ would prolong the rewarm time compared with a single arterial anastomosis and might adversely affect subsequent allograft function, since warm ischemic damage has been shown to be more crucial to subsequent allograft function than cold ischemia.[4] Kidneys that would be exposed to cyclosporine as part of the immunosuppression regimen are particularly vulnerable because prolonged warm ischemia appears to exacerbate the nephrotoxic effect of cyclosporine.[5] In addition to using kidneys with complicated vasculature, microvascular surgery has facilitated the use of some kidneys in which the vessels have been damaged during procurement. The surgeon might hesitate to use an immunologically compatible live donor with multiple renal arteries bilaterally if complicated in-situ anastomoses are required. However, with microvascular repair ex vivo, the subsequent in-situ anastomoses are much simpler.

Complications arising from the microvascular repair were negligible in this series of patients. Microvascular repair has several theoretical and technical advantages over other methods of handling allografts with multiple vessels and is a valuable adjunct to renal transplantation. The same microsurgical techniques are applicable in selected cases of renal autotransplantation.

References

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2. NOVICK AC, MAGNUSSON M, BRAUN WE: Multiple-artery renal transplantation: emphasis on extracorporeal methods of donor arterial reconstruction. *J Urol* 1979; 122: 731–735
3. BELZER FO, SCHWEIZER RT, KOUNTZ SL: Management of multiple vessels in renal transplantation. *Transplant Proc* 1972; 4: 639–644
4. SCOTT DF, STEPHENS FO, KEAVENY TV et al: Evaluation of preservation of cadaveric kidneys. *Transplantation* 1971; 11: 90–97
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PRESCRIBING INFORMATION

Rocephin® IV-IM

Sterile Ceftriaxone Sodium

For Injection

Therapeutic Classification

Antibiotic

INDICATIONS AND CLINICAL USES The treatment of the following infections when caused by susceptible strains of the designated micro-organisms: **Lower respiratory tract infections** caused by *E. coli, H. influenzae, K. pneumoniae* and species, *Staph. aureus, Strep. pneumoniae* and species (excluding enterococci). **Urinary tract infections (complicated and uncomplicated)** caused by *E. coli, Klebsiella* species, *P. mirabilis* and *P. vulgaris*. **Bacterial septicemia** caused by *E. coli, H. influenzae, K. pneumoniae, Staph. aureus* and *Strep. pneumoniae* (excluding enterococci). **Skin and skin structure infections** caused by *K. pneumoniae* and species, *P. mirabilis, Staph. aureus, Staph. epidermidis* and *Streptococcus* species (excluding enterococci). **Bone and joint infections** caused by *Staph. aureus, Strep. pneumoniae* and *Streptococcus* species (excluding enterococci). **Meningitis** caused by *H. influenzae, N. meningitidis*, and *Strep. pneumoniae*. 'Rocephin' should not be used for the treatment of meningitis caused by *L. monocytogenes*. **Uncomplicated gonorrhea (cervical/urethral and rectal)** caused by *N. gonorrhoeae* (penicillinase and nonpenicillinase producing strains). **Prophylaxis:** The preoperative administration of a single 1 g dose of 'Rocephin' (sterile ceftriaxone sodium) may reduce the incidence of postoperative infections in patients undergoing vaginal or abdominal hysterectomy. If signs of post surgical infection should appear, specimens for culture should be obtained for identification of the causative organism(s) so that the appropriate therapy may be instituted. **CONTRAINDICATIONS** 'Rocephin' (sterile ceftriaxone sodium) is contraindicated in patients with known allergy to ceftriaxone, other cephalosporins or penicillins. **WARNINGS** Before therapy with 'Rocephin' (sterile ceftriaxone sodium) is instituted, careful inquiry should be made concerning previous hypersensitivity reactions to ceftriaxone, other cephalosporins, penicillins or other allergens. 'Rocephin' should only be administered with caution to any patient who has demonstrated any form of allergy particularly to drugs. Serious, and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients receiving cephalosporins. The reactions are more likely to occur in persons with a history of sensitivity to multiple allergens. 'Rocephin' should be administered with caution to patients with type I hypersensitivity reaction to penicillin. If an allergic reaction occurs, the administration of 'Rocephin' should be discontinued and appropriate therapy instituted. Pseudomembranous colitis has been reported with the use of 'Rocephin', (and with broad-spectrum and other antibiotics). Therefore, it is important to consider its diagnosis in patients administered 'Rocephin' who develop diarrhea. Treatment with broad-spectrum antibiotics, including 'Rocephin', alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Mild cases of colitis may respond to drug discontinuation alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by discontinuation of 'Rocephin' administration or when it is severe, consideration should be given to the administration of vancomycin or other suitable therapy. Other possible causes of the colitis should also be considered. 'Rocephin' therapy should be discontinued in patients who develop signs or symptoms suggestive of gallbladder disease and conservative management considered. The effect of pre-existing gallbladder disease is not known. In a few patients administered 'Rocephin', shadows suggesting "sludge" have been detected by sonograms of the gallbladder in those who remained asymptomatic and in those who became symptomatic. This condition appeared to be reversible on discontinuation of 'Rocephin' therapy. In a few symptomatic patients receiving 4 g of 'Rocephin' who underwent cholecystectomy, "sludge" containing traces of ceftriaxone was recovered from surgical specimens. Concretions consisting of the precipitated calcium salt of ceftriaxone have been found in the gallbladder bile of dogs and baboons treated with high doses of ceftriaxone. **PRECAUTIONS General** Hypoprothrombinemia and alterations in prothrombin time have occurred rarely in patients treated with 'Rocephin' (sterile ceftriaxone sodium) (see ADVERSE REACTIONS). Patients with impaired vitamin K synthesis or low vitamin K stores (e.g. chronic hepatic disease and malnutrition) may require monitoring of hematology and coagulation parameters during 'Rocephin' treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during treatment. Prolonged treatment with 'Rocephin' may result in overgrowth of non-susceptible organisms and organisms initially sensitive to the drug. If superinfection occurs, appropriate measures should be taken. 'Rocephin' should be administered with caution to individuals with a history of gastrointestinal disease, particularly colitis. **Renal and Hepatic Impairment** Although transient elevations of BUN and serum creatinine have been observed in clinical studies, there is no other evidence that 'Rocephin', when administered alone, is nephrotoxic. In severe renal impairment (creatinine clearance of less than 10 mL/min), periodic monitoring of serum ceftriaxone concentrations is recommended. The maximum daily dose should not exceed 2 g. In severe renal impairment associated with clinically significant hepatic impairment, close monitoring of serum ceftriaxone concentrations, at regular intervals, is recommended. If there is evidence of accumulation, dosage should be decreased accordingly. **Interactions** Interactions between 'Rocephin' and other drugs have not been fully evaluated. **Pregnancy** The safety of 'Rocephin' in the treatment of infections during pregnancy has not been established. 'Rocephin' should only be used during pregnancy if the likely benefit outweighs the potential risk to the fetus and/or the mother. Ceftriaxone has been detected in the umbilical cord blood, amniotic fluid and placenta. **Nursing Mothers** Ceftriaxone is excreted in human milk at low concentrations. The clinical significance of this is unknown; therefore, caution should be exercised when 'Rocephin' is administered to a nursing mother. **Neonates** The safety of 'Rocephin' in neonates (birth to one month of age) has not been established. *In vitro* studies have shown that ceftriaxone can displace bilirubin from serum albumin. Caution should be exercised when considering 'Rocephin' treatment for hyperbilirubinemic neonates especially if premature. **Elderly Patients** The elimination of ceftriaxone may be reduced in elderly patients possibly due to impairment of both renal and hepatic function. **Drug-Laboratory Test Interactions** Ceftriaxone may interfere with urine glucose determinations utilizing the copper-reduction test (CLINITEST), but not utilizing the glucose-oxidase test (DIASTIX or TES-TAPE) **ADVERSE REACTIONS** During clinical trials with 'Rocephin' (sterile ceftriaxone sodium) the following adverse reactions have been observed: **Clinical Adverse Experiences: Dermatological**: Rash (1.3%); exanthema, allergic dermatitis and pruritis (0.1 - 1.0%). **Hematological**: Anemia (0.1 - 1.0%); auto-immune hemolytic anemia and serum sickness (<0.1%). **Hepatic**: Jaundice, reports (in asymtomatic and symptomatic patients) of ultrasonographic shadows suggesting precipitations in the gallbladder and reports of gallbladder sludge (<0.1%). **Urogenital**: Moniliasis and vaginitis (0.1 - 1.0%). **Gastrointestinal**: Diarrhea (3.3%); nausea, vomiting, dysgeusia and gastric pain (0.1 - 1.0%); abdominal pain, colitis, flatulence, dyspepsia, pseudomembranous colitis and stomatitis (<0.1%). **Neurological**: Dizziness and headache (0.1 - 1.0%); ataxia and paresthesia (<0.1%). **Miscellaneous**: Fever, chills, diaphoresis, malaise, burning tongue, flushing, edema and anaphylactic shock (0.1 - 1.0%); bronchospasm, palpitations and epistaxis (<0.1%). **Local Reactions at Injection Site**: Pain (9.4%), induration and tenderness (1-2%); phlebitic reactions (0.1 - 1.0%); thrombophlebitis (<0.1%). **Laboratory Abnormalities**: **Hematologic**: Eosinophilia (4.6%), thrombocytosis (5.1%), leukopenia (2.0%); neutropenia, lymphophenia, thrombocytopenia, increase or decrease in hematocrit, prolongation of prothrombin time and decrease in hemoglobin (0.1 - 1.0%); leukocytosis, lymphocytosis, monocytosis, basophilia and decrease in prothrombin time (<0.1%). **Hepatic**: Increase in AST (SGOT) (4.0%)[b], ALT (SGPT) (4.8%)[b], increase in alkaline phosphatase (1.0%); increase in bilirubin (0.1 - 1.0%). **Urinary**: Increase in BUN (1.1%)[c]; increase in creatinine, erythrocyturia, proteinuria and presence of casts in urine (0.1 - 1.0%); glycosuria (<0.1%). [b] Incidence is more frequent in patients less than one year old. [c] Incidence is more frequent in patients less than one year old and over 50 years old. **SYMPTOMS AND TREATMENT OF OVERDOSAGE** Ultrasonographic shadows suggesting precipitations in the kidneys accompanied by calcium ceftriaxone precipitate in the urine was observed in one patient dosed with 'Rocephin' (sterile ceftriaxone sodium) at 10 g/day (2.5 times the maximum recommended dose). No other case of overdosage has been reported to date with 'Rocephin'. No specific information on symptoms or treatment is available. Excessive serum concentration of ceftriaxone cannot be reduced by hemodialysis or peritoneal dialysis. Treatment should be symptomatic. **DOSAGE AND ADMINISTRATION** 'Rocephin' (sterile ceftriaxone sodium) may be administered intravenously or intramuscularly after reconstitution. Dosage and route of administration should be determined by the severity of infection, susceptibility of the causative organisms, and condition of the patient. The intravenous route is preferable for patients with septicemia or other severe or life-threatening infections. With the exception of gonorrhea, which is treated with a single dose, the administration of 'Rocephin' should be continued for a minimum of 48 to 72 hours after the patient defervesces or after evidence of bacterial eradication has been obtained, usually 4 to 14 days. In bone and joint infections the average duration of treatment during clinical trials was 6 weeks, with a range of 1 to 13 weeks, depending on the severity of the infection. When treating infections caused by beta-hemolytic *Streptococcus*, it is recommended that therapy be continued for at least 10 days. The average duration of therapy for infections associated with beta-hemolytic *Streptococcus* during clinical trials was 2 weeks, with a range of 1 to 5 weeks, depending on the site and severity of the infection. **Prophylaxis (Vaginal or Abdominal Hysterectomy)** For preoperative use as prophylaxis before vaginal or abdominal hysterectomy, a single dose of 1 g administered 1/2 to 2 hours before surgery is recommended. **Impairment of Renal and/or Hepatic Function** In patients with mild to moderate renal impairment, changes in the dosage regimen are not required, **provided liver function is intact**. In cases of preterminal renal failure (creatinine clearance less than 10 mL/min), periodic monitoring of serum ceftriaxone concentrations is recommended. The daily dosage should be limited to 2 g or less. In patients with liver damage, there is no need for the dosage to be reduced **provided renal function is intact**. In cases of coexistent renal and clinically significant hepatic insufficiency, close monitoring of serum ceftriaxone concentrations, at regular intervals, is recommended. If there is evidence of accumulation, dosage should be decreased accordingly. **ADMINISTRATION Intramuscular**: The reconstituted solution of 'Rocephin' should be administered by deep intragluteal injection. It is recommended that not more than 1 g be injected at a single site. Pain on intramuscular injection is usually mild and less frequent when 'Rocephin' is administered in sterile 1% Lidocaine solution. **Intravenous (bolus) Injection**: The reconstituted solution should be administered over approximately 5 minutes. **Short Intravenous Infusion**: The further diluted intravenous solution should be given over a period of 10 to 15 minutes in infants and children and 20 to 30 minutes in adults. **NOTE**: 'Rocephin' solution should not be physically mixed with aminoglycoside antibiotics nor administered at the same site because of possible chemical incompatibility.

PHARMACEUTICAL INFORMATION

Reconstitution

For Intramuscular Use

Reconstitute 'Rocephin' powder with the appropriate diluent:

- Sterile Water for Injection
- Bacteriostatic Water for Injection
- 0.9% Sodium Chloride Injection
- 1% Lidocaine Solution
- 5% Dextrose Injection

Reconstitute as follows:

Reconstitution Table (IM)

Vial Size	Volume to be added to vial mL	Approximate available volume mL	Approximate average concentration g/mL
0.25 g	0.9	1	0.25
0.5 g	1.8	2	0.25
1.0 g	3.6	4	0.25
2.0 g	7.2	8	0.25

Shake well until dissolved.

NOTE: SOLUTIONS PREPARED FOR INTRAMUSCULAR USE OR ANY SOLUTION CONTAINING LIDOCAINE OR BACTERIOSTATIC WATER FOR INJECTION SHOULD NEVER BE ADMINISTERED INTRAVENOUSLY.

For Intravenous Use

Reconstitute only with Sterile Water for Injection.

Reconstitute as follows:

Reconstitution Table (IV)

Vial Size	Volume to be added to vial mL	Approximate available volume mL	Approximate average concentration g/mL
0.25 g	2.4	2.5	0.1
0.5 g	4.8	5.0	0.1
1.0 g	9.6	10.0	0.1
2.0 g	19.2	20.0	0.1

Shake well until dissolved. The prepared solution may be further diluted to the desired volume with any of the "Solutions for IV Infusion" listed below.

Solutions for IV Infusion

0.9% Sodium Chloride Injection, 5% Dextrose Injection, Dextrose and Sodium Chloride Injection.

Pharmacy Bulk Package Reconstitution for Preparation of Intravenous Infusion Solutions

The closure of the pharmacy bulk vial shall be penetrated only one time after reconstitution, using a suitable sterile transfer device or dispensing set which allows measured dispensing for the contents.

Reconstitution Table for Bulk Pharmacy Package

Vial size	Volume to be added to vial mL	Approximate available volume mL	Approximate average concentration g/mL
10 g	95	100.0	0.1

Shake well until dissolved. Withdraw the required amount and dilute with one of the "Solutions for IV Infusion". Any unused solution remaining within a period of 8 hours should be discarded.

Stability of Solutions - Storage

For complete stability and storage information, consult the Product Monograph.

Incompatibility:

'Rocephin' should not be physically mixed with other antimicrobial agents.

'Rocephin' should not be added to blood products, protein hydrolysates or amino acids.

'Rocephin' should not be added to solutions containing calcium.

DOSAGE FORM

Availability: 'Rocephin' is available in vials containing dry substance equivalent to 0.25 g, 0.5 g, 1 g or 2 g of ceftriaxone and as a pharmacy bulk vial containing the equivalent of 10 g ceftriaxone (not for direct administration). *The availability of the Pharmacy bulk vial is restricted to hospitals with a recognized intravenous admixture program.*

Storage: 'Rocephin' sterile powder should be stored at a controlled room temperature (between 15° and 30°C) and protected from light.

References: 1. Hell K: Chemotherapy 1989;**35**:228-235. **2.** 'Rocephin' Product Monograph.

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Original Research in Medicine and Chemistry

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Comparison of Automated and Manual Methods for Islet Isolation

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The authors used the principal features of a collagenase perfusion technique and an automated dissociation technique to determine if islets could be isolated from the large mammal pancreas and to compare the effects of the two methods on isolated islets. The pancreases of 16 dogs were cannulated and perfused with collagenase at 4°C, then warmed to 37°C. Group 1 (eight) pancreases were perfused at 37°C until digested, then dissociated manually by teasing and trituration. Group 2 (eight) pancreases were transferred to a closed chamber for continued collagenase digestion and dissociation at 37°C. Islets were purified using identical Ficoll gradients. Aliquots were stained with dithizone and evaluated for number, size and purity. Total islet volume was calculated.

Group 2 pancreases were thoroughly digested leaving only a few residual ducts, but undigested fragments persisted in group 1 pancreases. Islet size was similar in both groups. There was a greater islet volume before and after Ficoll purification in group 2, but the difference was not significant. Purity was greater than 90% in both groups. Perifusion with 28 mM glucose elicited a biphasic insulin release from islets in both groups.

The data show that the combined protocol enables mass isolation of purified islets from the canine pancreas. Compared with the manual technique, the automated protocol for pancreas dissociation tends to improve the yield of islets without compromising islet size and viability. It provides the advantages of a closed system with increased control over the extent of collagenase digestion.

Afin de déterminer si les îlots pancréatiques pouvaient être isolés du pancréas des gros mammifères et d'apprécier les effets des techniques manuelle et automatisée d'isolation des îlots, les auteurs ont associé les principales caractéristiques d'une technique de perfusion à la collagénase mise au point dans leur laboratoire et une technique automatisée. Les canaux pancréatiques de 16 chiens ont été canulés et perfusés avec de la collagénase à 4°C, avec réchauffement subséquent à 37°C. Les (huit) pancréas du groupe 1 ont été perfusées à 37°C jusqu'à digestion complète, puis dissociés manuellement par effilochage et trituration. Les (huit) pancréas du groupe 2 ont été transférés en vase clos pour la poursuite de la digestion à la collagénase combinée à une dissociation à 37°C. Les îlots ont ensuite été purifiés à l'aide de gradients Ficoll identiques. Des aliquotes ont été colorées à la dithizone puis exminées pour en évaluer le nombre, la taille et la pureté. Le volume total d'îlots fut aussi calculé.

Les pancréas du groupe 2 étaient complètement digérés, ne laissant que quelques canaux résiduels, alors que des fragment non digérés persistaient dans le groupe 1. La distribution selon la taille était semblale pour les deux groupes. Le volume des îlots avant et après purification par gradients Ficoll ne différait pas de façon importante. La pureté était supérieure à 90% dans les deux groupes. Une périfusion à l'aide 28 mM de glucose a provoqué une libération biphasique d'insuline dans les deux cas.

Ces données démontrent qu'il est possible d'isoler de grandes quantités d'îlots purifiés de pancréas canin à l'aide de ce protocole combiné. Comparativement à la technique manuelle, le protocole automatisé de dissociation pancréatique a augmenté le rendement d'isolation des îlots sans compromettre leur taille ou leur viabilité, bien que cette augmentation n'ait pas été significative. Cette méthode offre les avantages d'un système fermé avec un meilleur contrôle du degré de digestion à la collagénase.

Progress in the isolation of islets of Langerhans from the pancreas of adult human organ donors[1–3] has promoted studies of pancreatic islet transplantation in insulin-dependent diabetes mellitus.[4,5] However, results of renewed trials suggest that yields of islets must be optimized to reverse the insulin-dependent state. Improvements can be made in three key steps that form the basis for islet isolation protocols: collagenase digestion of the fibrous connective tissue stroma of the pancreas; gentle mechanical dissociation of islets from exocrine constituents; and purification. Although the optimal protocol to be followed has not been defined, two recently described methods for collagenase digestion appear promising. We have perfused collagenase through canine or human pancreatic ducts, gently dissociated the pancreas with manual teasing and tritu-

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ration and purified islets with Ficoll gradients.[2,6]

Ricordi and colleagues[3] have reported success with human islet isolation using an automated technique that simultaneously subjects the pancreas to collagenase digestion and dissociation. In the present study we combined the principal features of the collagenase perfusion method with the automated digestion technique. The canine pancreas was used because its structure and collagen distribution approximate those observed in the human pancreas. Our aim was to determine if islets could be isolated from the canine pancreas using this combined protocol and to compare the effects of manual or automated isolation on the size, viability, purity and yield of canine islets.

Material and Methods

Islet Isolation

The pancreases of 16 dogs were mobilized, preserving all major vascular connections. Both main branches of the pancreatic duct were cannulated in situ using 20-gauge cannulas. The gland was then excised and weighed. A third cannula was inserted into the left duct 5 cm from the tip of the gland. Hanks' solution (50 ml) containing collagenase (Sigma Type XI; Sigma Co., St. Louis, Mo., 1100 U/ml at 4°C) was injected slowly into each cannula. For digestion, each cannula was connected to a perfusion device and perfused with collagenase solution (6 ml/g of original pancreas weight, 1100 U/ml) at 4°C for 10 minutes. The perfusate was warmed at a rate of 3°C/min to 37°C. Figure 1 summarizes the two types of protocols that were followed for subsequent islet isolation.

Group 1 (eight) pancreases were perfused until the gland became mucoid (approximately 10 to 12 minutes after commencement of warming). The pancreas was then cooled to 4°C and dissociated by teasing and trituration. Group 2 (eight) pancreases were transferred to an oscillating chamber (3 Hz) for digestion with collagenase (same dose as above) and dissociation at 37°C. Islets that were liberated in the chamber were continuously collected from the effluent of solution that flowed through the chamber and cooled to 4°C.[3] Final purification was performed with Ficoll using gradient densities of 1.045, 1.075 and 1.085 as previously described.[7,8]

Quantification of Islets

Aliquots of the islet suspension were stained with dithizone and

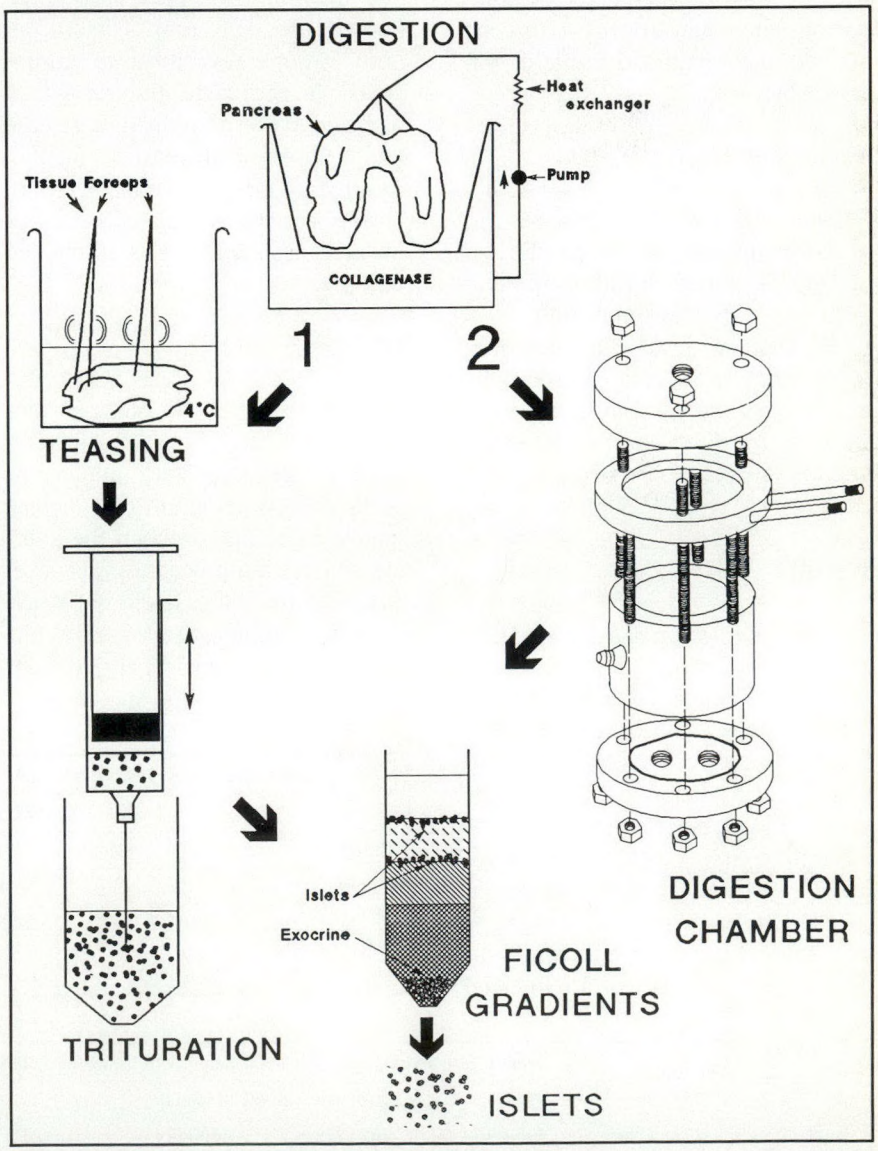

FIG. 1. Comparison of two protocols. All pancreases were initially perfused with collagenase through three cannulas inserted into pancreatic ducts. Pancreas was then dissociated by manual (group 1, teasing and trituration) or automated (group 2, digestion chamber) method. In each case, islets were purified using Ficoll gradients.

examined microscopically. The numbers of islets in each size range of 60 to 99 μm, 100 to 149 μm, 150 to 199 μm, 200 to 249 μm and greater than 250 μm in diameter were counted with the aid of an optical graticule and converted to a number of islets with a standard diameter of 150 μm. The number of islets equivalent to 150 μm in diameter was multiplied by a volume constant to calculate the volume of islets. Purity was estimated by comparing the quantity of dithizone stained and unstained tissue at microscopy.

Viability of Islets

Islet viability was assessed in vitro by measuring the insulin secretory response during perifusion with low (2.8 mM), and high (27.8 mM) glucose levels. In addition, islets from five group 1 isolations and from one group 2 isolation were autografted to the spleen by venous reflux.

Results

Pancreas Digestion and Dissociation

Group 2 pancreases were thoroughly digested into fine particles, leaving a few residual ducts but no exocrine particles. In contrast, group 1 pancreases were dissociated into coarse particles which required trituration with 14-gauge needle (three times), a 16-gauge needle (three times) and an 18-gauge needle (twice). Undigested fragments persisted, comprising 22% of the original pancreas weight.

Islet Size and Viability

Table I shows that the size range of the islets is similar in both groups, the majority of the islets being in the lower range (60 to 99 μm diameter), but in group 2 a larger proportion of islets were identified in the upper size range (more than 150 μm). Islets from both groups responded to an increase in perifusate glucose with a biphasic pattern of insulin release and a threefold increase in insulin. The magnitude of insulin secretion, both basal and stimulated, was less in islets isolated by the automated method.

Islet Yield

Table II shows the islet recovery before and after Ficoll purification in both groups. The number of islets yielded per gram of pancreas tended to be higher when the automated isolation procedure was used, although the increase did not reach statistical significance (Mann–Whitney test). Similarly, when the islet yield was expressed in terms of volume, the automated technique appeared to provide a greater yield, although again statistical significance was not achieved. Ficoll purification resulted in a 52% reduction of islet volume in group 1 compared with a 42% reduction in group 2. Purity was greater than 90% in both groups.

Weight-Corrected Islet Yields and Implantation

The final mean (± standard error) pure islet volume (μL/kg donor body weight) was 4.4 ± 1.5 in group 1 compared with 7.6 ± 1.6 in group 2. Normoglycemia ensued when more than 4 μL/kg of purified islets were autoimplanted after preparation with the manual (five pancreases) or automated (one pancreas) technique.

Discussion

Initial clinical experience with islet transplantation suggests that an adult patient with insulin-dependent (type I) diabetes will require more than 3710 islets of mean diameter 150 μm/kg body weight to reverse insulin dependence.[5] This represents an estimat-

Table II. Yields of Islets Isolated With Manual or Automated Methods*

		No. of islets, X 10^3/g		Volume of islets, μL/g	
Group	No.	Pre-Ficoll	Post-Ficoll	Pre-Ficoll	Post-Ficoll
Manual	8	4.8 ± 1.0	3.0 ± 0.7	4.2 ± 1.0	2.0 ± 0.7
Automated	8	7.3 ± 1.0†	3.7 ± 0.7†	6.2 ± 1.4†	3.6 ± 0.8†

*Mean ± SEM.
†Not significant versus manual.

Table I. Size and Viability of Islets Isolated With Manual or Automated Methods*

		Islet size, μm (% of islets)				Insulin secretion, μU/islet · min^{-1}	
Group	No.	60–99	100–149	150–199	>200	Basal	Stimulated
Manual	8	64 ± 3	32 ± 2	4 ± 1	0.4 ± 0.3	0.03 ± 0.01	0.11 ± 0.02†
Automated	8	61 ± 6	29 ± 4	8 ± 3	2 ± 1	0.01 ± 0.003	0.03 ± 0.007†

*Mean ± SEM.
†Threefold rise over basal level.

ed islet volume of more than 6.5 μL/kg. The quantity may need to be augmented further to provide the critical mass of β-cells,[7] as well as to overcome the potential deleterious effects of reduced viability, immunosuppressive drugs,[9] the diabetic state,[10] the site chosen for implantation[11] and rejection or autoimmune phenomena. Islet yields of this magnitude have recently been reported.[2,3] However, recovery continues to vary in different isolations, and the optimal method for islet preparation needs to be defined.

In earlier studies we found that collagenase perfusion through the pancreatic duct was superior to ductal injection for isolating islets from the human pancreas.[2] Perfusion appeared to enhance the delivery of collagenase to the intralobular exocrine compartment of the pancreas, thereby improving the cleavage of connective tissue stroma, which binds the islets. Ricordi and colleagues[3] used a duct injection technique, then developed an automated method to liberate large quantities of human islets. Among the advantages they cited were minimal trauma to the islets, continuous liberation from collagenase, which protects islets from excessive digestion, and minimal human intervention. In this study, we combined the advantages of both perfusion and automation. The result was successful isolation of mass quantities of islets from the canine pancreas, which compares favourably with results of other studies, including our own.[6,8,12] The quantity of pure islets provided per unit body weight of donor (7.6 μL/kg) is well in excess of that which we found necessary for consistent reversal of hyperglycemia (more than 4.5 μL) after autoimplantation.[7] This quantity also compares favourably with the quantity of islet tissue that we predict is necessary to induce normoglycemia in human recipients.

Comparison of results of the manual and automated methods of islet isolation revealed that the quantity of islets isolated was consistently better using the latter method, although the improvement in yields did not reach statistical significance. A comparison of morphology and viability of the islets isolated revealed that islets of similar size can be obtained by either method, and the response to perifusate glucose showed a threefold rise in each case. Although the quantity of insulin released was less in the automated studies, this could be attributed to such factors as a reduced size of the islets in the sample subjected to perifusion.[2]

Some additional factors regarding the combined procedure are noteworthy. First, the digestion chamber augments the activity of collagenase delivered to the intralobular environment by incubating the periphery of undigested particles for longer. Thus, we found that the duration of exposure to collagenase at 37°C could be increased from 10 minutes to more than 25 minutes, which may have freed more entrapped islets. Second, the automated procedure provided the advantage of a closed system, which reduced the likelihood of bacterial or fungal contamination. It should also be noted that the quantity of collagenase solution needed to operate the digestion chamber was twice that used for the perfusion method alone.

In summary, these data show that the combination of an automated digestion protocol and collagenase ductal perfusion enabled mass isolation of purified islets from the canine pancreas. Comparison of the manual and automated protocols shows that automation tends to improve yields of islets without compromising islet morphology and viability, although the yields are not significantly higher. The modification provides the advantages of a closed system with control over the extent of collagenase digestion. This protocol may provide improved isolation of islets from the human pancreas.

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5-aminosalicylic acid (5-ASA) is considered to be the active component of sulfasalazine. Although its mode of action has not been definitely elucidated, 5-ASA is thought to have a topical anti-inflammatory effect which is produced by inhibition of prostaglandin and/or leukotriene synthesis.

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Detectable plasma levels of 5-ASA were seen 4 hours after a single oral dose of tablets (2 x 250 mg). Peak plasma levels of 5-ASA and N-acetyl-5-ASA were 1.2 and 1.9 μg/mL, respectively, and occurred 6.5 - 7 hours post-dosing. Mean steady-state plasma levels of 5-ASA and N-acetyl-5-ASA using a 500 mg t.i.d. dosage schedule are 0.7 and 1.2 μg/mL, respectively.

Except for a delay of 1.5 - 3 hours in time to peak of 5-ASA and N-acetyl-5-ASA plasma levels, Mesasal™ pharmacokinetics are essentially the same in fasted and fed subjects.

INDICATIONS

Mesasal™ (5-aminosalicylic acid) tablets are indicated in the management of acute ulcerative colitis, and for the prevention of relapse of active ulcerative colitis.

CONTRAINDICATIONS

Mesasal™ (5-aminosalicylic acid) is contraindicated where there is a history of hypersensitivity to salicylates.

Mesasal™ is contraindicated in cases of hemorrhagic diathesis.

Mesasal™ is contraindicated in patients with existing gastric and duodenal ulcers.

Mesasal™ is contraindicated in patients with urinary tract obstruction.

WARNINGS

In cases of severe liver and kidney disorders, caution should be exercised.

Use in Pregnancy:

In the first three months of pregnancy, treatment is recommended only if potential benefits outweigh the possible risks.

Pediatric Use:

There is no experience with respect to the use of this drug in children; potential benefits should be weighed against possible risks.

PRECAUTIONS

Drug Interactions:

The blood-sugar reducing effect of sulfonyl ureas may be enhanced. Interactions with coumarins, methotrexate, probenecid, sulfinpyrazone, spironolactone, furosemide and rifampicin cannot be excluded. Potentiation of undesirable glucocorticoid effects on the stomach is possible.

In long term therapy, periodic urinalysis should be conducted. Caution should be exercised when therapy is first initiated in patients known to be allergic to sulfasalazine.

ADVERSE REACTIONS

In controlled clinical trials in 395 patients who received 5-ASA, the following adverse reactions were reported: headache (3.04%), nausea (2.03%), abdominal pain (1.52%), and diarrhea (1.52%). Other adverse effects common to salicylates, including hypersensitivity reactions, may be expected to occur rarely. There have been a few spontaneous reports of pancreatitis, acute and chronic interstitial nephritis and pericarditis, associated with 5-ASA therapy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no specific antidote. Gastric lavage should be employed, followed by promotion of diuresis by the intravenous infusion of an electrolytic solution.

DOSAGE AND ADMINISTRATION

During the acute inflammatory stage and in long-term maintenance therapy, Mesasal™ (5-aminosalicylic acid) must be taken reliably and consistently by the patient in order to ensure therapeutic success.

Although symptomatic relief may be seen as early as three to twenty-one days, therapy should be continued depending on clinical findings.

The following dosage regimens are recommended:

Adults

Tablets: For the management of acute ulcerative colitis: 1.5 g to 3 g daily in divided doses. **For prevention of relapses of acute ulcerative colitis:** 1.5 g daily in divided doses.

AVAILABILITY AND STORAGE

Tablets

Mesasal™ enteric coated tablets, 250 mg and 500 mg, are available in amber glass bottles of 100 tablets. Mesasal™ tablets should be swallowed whole before meals with plenty of fluid.

Vagotomy and Antrectomy Revisited

C. Kotwall, MD, MSc, FRCSC; H.T.G. Williams, MD, FRCS, FRCSC

A retrospective review of 185 patients who underwent truncal vagotomy and antrectomy for duodenal ulcer disease was carried out to determine the mortality and morbidity of the procedure. There were no deaths within 30 days of operation and only one patient died while in the hospital (0.54%). Twenty-one patients (11.4%) suffered early morbidity, 3 of them requiring a second operation. Follow-up was obtained in 83 patients and averaged 13.5 years. According to Visick's classification 75 patients (90.4%) were in class I or II; 5 patients (6%) were in class III and 3 patients (3.6%) in class IV.

A recurrent ulcer developed in 2 of the 83 patients. In contrast, after highly selective vagotomy, the literature supports an unacceptable incidence of recurrent ulcer. Therefore, we must not prematurely cast aside vagotomy and antrectomy; it still remains a safe and acceptable procedure for duodenal ulcer disease.

Cette étude rétrospective de 185 patients, qui ont subi une vagotomie tronculaire avec antrectomie pour ulcère duodénal, a été réalisée dans le but d'établir la mortalité et la morbidité reliées à cette intervention. Aucun décès n'a été enregistré dans les 30 jours qui ont suivi l'opération et un seul patient (0.54%) est décédé durant son hospitalisation. Vingt-et-un patients (11.4%) ont souffert d'une morbidité précoce, 3 d'entre-eux nécessitant une seconde opération. Un suivi a pu être obtenu pour 83 patients et sa durée moyenne a été de 13.5 années. Soixante-quinze patients (90.4%) appartenaient aux classes I et II de la classification de Visick; 5 patients (6%) étaient dans la classe III et 3 (3.6%) dans la classe IV.

Une récidive de l'ulcère est apparue chez 2 des 83 patients. En comparaison, la littérature médicale rapporte une incidence inacceptable d'ulcères récidivants après vagotomie très sélective. Il ne faut donc pas rejeter prématurément la vagotomie-antrectomie; elle demeure une opération sûre et acceptable pour l'ulcère duodénal.

The place of truncal vagotomy and antrectomy in the modern-day treatment of duodenal ulcer disease is unclear. There is a plethora of reports in the literature attesting to the advantages of highly selective vagotomy over any other ulcer operation, in both prospectively randomized[1-6] and retrospective studies.[7-13] But all these studies report an incidence of recurrent ulcer ranging from 3.5% to 30%, with varying periods of follow-up.

Dissatisfaction with highly selective vagotomy has led to such innovative procedures as proximal gastric vagotomy and mucosal antrectomy.[14] In addition, the advent of H_2-receptor antagonists has altered the role of surgical therapy.

In this study we review the mortality, morbidity (early and long-term) and incidence of recurrent ulcer in truncal vagotomy and antrectomy, done by a single surgeon (H.T.G.W.) over a 16-year period. In the light of highly selective vagotomy, we will then try to reassess the role of vagotomy and antrectomy in duodenal ulcer disease.

Patients and Methods

We reviewed retrospectively 185 consecutive patients (135 men, 50 women) with duodenal ulcer disease who underwent truncal vagotomy and antrectomy between 1960 and 1976. The mean age of the patients was 47.4 years. All patients with gastric ulcer were excluded. Preoperative investigations included barium studies in most patients; gastric acid analysis was performed in no more than 15%. Forty-one patients (22.2%) were identified as having undergone 43 previous surgical procedures for their duodenal ulcer diathesis (Table I). The most common antecedent surgical procedure was a Rosco-Graham patching for a perforated duodenal ulcer. The average interval between the previous surgical procedure and vagotomy and antrectomy was 6.2 years. Indications for vagotomy and antrectomy included intractability in 113

Table I. Surgical Procedures Performed Prior to Vagotomy and Antrectomy

Procedure	No. of procedures
Perforated duodenal ulcer (patching)	20
Partial gastrectomy with	
Billroth II	10
Billroth I	2
Vagotomy and pyloroplasty	8
Gastrojejunostomy	2
Vagotomy and gastrojejunostomy	1
Total	43

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(61.1%), bleeding in 34 (18.4%), obstruction in 28 (15.1%) and perforation in 2 (1.1%).

The operative technique is as follows: after a nasogastric tube has been inserted, a bilateral truncal vagotomy is performed. The left triangular ligament of the liver may be incised to retract the lateral segment of the left lobe for additional exposure, but the use of a Weinberg retractor is usually sufficient. The esophagus is mobilized on the right and left aspects, carefully retaining the dorsal attachment of "mesoesophagus" in which lies the posterior vagus trunk. Sliding this tissue between the finger and thumb, working anteriorly from the aorta, makes identification of the posterior vagus relatively easy. Metal clips are placed on it, approximately 3 cm apart, and the intervening segment is sent for pathological examination. Traction is then placed on the esophagus with a Penrose drain, and the left (anterior) vagal trunk is identified lying on the anterior esophageal musculature; in similar fashion, a segment is sent for examination. A meticulous search is then made for any other accessory vagal fibres which, if found, are divided.

Attention is then turned to the stomach where the distal one-half of the greater curvature is mobilized from the gastroepiploic vessels. The gastrohepatic ligament is divided in an avascular place and the descending branches of the left gastric artery are identified, doubly ligated proximally and divided. The right gastric artery is similarly ligated and divided. The line of transection of the stomach is from the mid-point of the greater curvature to a point just below the descending branch of the left gastric artery (approximately 3 cm above the gastric notch) to include the "tongue of antrum", which extends for a variable distance along the lesser curvature of the stomach (Fig. 1). A crushing clamp is then placed across the stomach at the line of transection. The stomach is divided 5 mm proximal to the clamp, first cutting down (with a new blade) to the vascular plexus in the submucosa, clamping the vessels and then dividing into the lumen. The divided stomach, with bleeding accurately controlled, is closed with a single layer of 3-0 silk interrupted sutures, starting at the lesser curvature and leaving a 7-cm opening at the greater curvature.

The duodenum is mobilized just beyond the pylorus and divided at this level, controlling the vessels in the submucosa. A finger is passed down the duodenum to assess any fibrous stenosis associated with the ulcer and to identify the ampulla of Vater. Any stenosis is relieved with a 5-cm incision down the anteromedial aspect of the duodenum. Gastroduodenostomy is then performed using a single layer of interrupted silk sutures and taking the greater curvature of the stomach to the apex of the anteromedial incision. A large posterior penetrating ulcer is entered when the duodenum is mobilized beyond the pylorus. The ulcer is excluded by using the distal margin for part of the anastomosis.

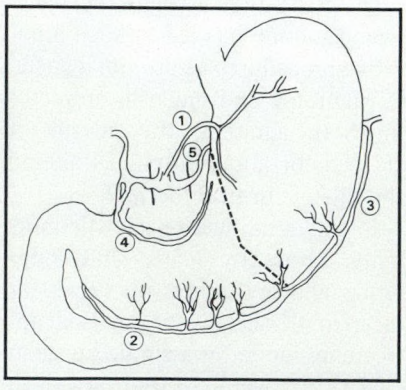

FIG. 1. Diagram of stomach showing line of transection from midpoint of greater curvature toward lesser curvature just below descending branch of left gastric artery. 1 = left gastric artery, 2 = right gastroepiploic artery, 3 = left gastroepiploic artery, 4 = right gastric artery, 5 = splenic artery.

Follow-up was obtained in 83 of the 185 patients (44.9%). The average duration of follow-up was 13.5 years. The method of follow-up was by telephone conversation between the junior author (C.K.) and the patient or, if the patient was not available or had died, a relative. Specific questions involved those related to dumping, diarrhea, weight loss, recurrent ulcer and overall success of the operation. A modified Visick score was used to categorize the patient's postoperative status: grade I — was no postoperative symptoms; grade II — mild symptoms that were controlled with dietary change and did not interfere with life-style; grade III — moderate symptoms requiring diet change and treatment, with incomplete control of the symptoms but with no serious change in life-style and grade IV — severe symptoms incompletely controlled by any treatment and with a major change in life-style; this category included all recurrent ulcers.

Results

After truncal vagotomy and antrectomy, gastroduodenostomy was performed in 175 (95.7%) patients; the remaining 8 had Billroth II gastrojejunostomy.

There were four incidental splenectomies (2.2%).

Complications

There were 21 major complications in 185 patients, an overall morbidity of 11.4% (Table II). Three of these complications required another operative procedure. The patient with gastric outlet obstruction subsequently required a gastrojejunostomy; in another patient a

Billroth II stomal obstruction developed secondary to twisting of the afferent and efferent loops, requiring operative intervention. The third patient had an anastomotic leak and required drainage of a subhepatic abscess. This patient was on hyperalimentation when *Candida* sepsis developed; this was followed by jaundice then subacute hepatic necrosis and she died 147 days after the vagotomy and antrectomy. Overall mortality was therefore 0.54%; however, there were no deaths within 30 days of operation.

Visick Scores

Table III lists the Visick scores for the 83 patients who were available for follow-up; 90.4% of the patients were placed in Visick grades I and II. Six patients had diarrhea and four had postoperative dumping. Of these 10 patients, 3 were Visick grade II, 5 were grade III and 2 were grade IV. One of the grade IV patients had Visick grade III diarrhea, but was changed to Visick IV when a recurrent ulcer developed. A second patient who was taking nonsteroidal anti-inflammatory medication suffered recurrent ulceration 14 years after the vagotomy and antrectomy; a 3-cm ulcer developed on the posterior wall of the gastroduodenostomy. The ulcer healed with cimetidine therapy, but gastric outlet obstruction developed necessitating gastroduodenoplasty. The rate of ulcer recurrence in these 83 patients was therefore 2.4%.

Table II. Morbidity of Vagotomy and Antrectomy

Morbidity	No.
Splenectomy	4
Wound infection	4
Pneumonia	4
Pulmonary embolism	4
Anastomotic leak	2
Gastric outlet obstruction	1
Pancreatitis	1
Billroth II stomal obstruction	1
Total	21

Table III. Visick Score (Modified)

Visick grade	No.	%
I	56	67.5
II	19	22.9
III	5	6.0
IV	3	3.6
Total	83	100.0

Discussion

There was no 30-day operative mortality in this study, but one patient died 147 days after surgery, and death was directly attributable to the gastric resection, giving an overall in-hospital mortality of 0.54%. This is somewhat lower than the 30-day operative mortality rates reported by Palumbo and Sharpe[15] and Hubert and colleagues[16] of 2.2% and 1.1% respectively, and the combined in-hospital and 30-day rate reported by Herrington, Sawyers and Scott[17] of 1.6% in 3584 patients. The majority of studies of highly selective vagotomy report no mortality;[1-8,10,12,13] Herrington, Davidson and Shumway[9] and Kennedy[11] cited rates of 0.7% and 0.3%, respectively, in a total of 435 patients who underwent highly selective vagotomy. It would appear that highly selective vagotomy is the operation of choice if mortality is the only end-point.

It is unfortunate that less than 50% of our patients could be contacted for follow-up after vagotomy and antrectomy. Reasons may include the retrospective nature of the study, the length of follow-up with an average of over 13 years, the lack of a need for continued medical visits (unlike carcinoma) and the transient nature of the population. Nevertheless, in our opinion it is important to report our recurrence rate and Visick status, realizing that over 50% of the patients could not be contacted.

The recurrence rate in this study for 83 patients who underwent vagotomy and antrectomy and were followed for an average of 13.5 years was 2.4%. One of these patients suffered a recurrence 14 years after operation, stressing the importance of long-term follow-up. Low recurrence rates after truncal vagotomy and antrectomy have been confirmed in three large series, comprising 4661 patients, with an ulcer recurrence rate ranging from 0.6% to 0.7%.[15-17] The follow-up of this large group of patients was approximately 10 years. In contrast, recurrent ulcer rates after highly selective vagotomy are variable and significantly higher than those after vagotomy and antrectomy. Hoffmann, Olesen and Jensen[7] from Copenhagen prospectively followed up 106 patients after parietal cell vagotomy; 30% of the patients had proven recurrent ulcers and a further 9% had suspected recurrence. Of the 32 proven ulcer recurrences, 10 developed within 5 years, 9 within 5 to 10 years and 13 developed 10 to 17 years after surgery. In addition, this report is from one of the institutions that pioneered highly selective vagotomy in 1970.[18] Vagotomy and antrectomy, therefore, remains clearly the operation of choice if ulcer recurrence is the only end-point.

Regarding postoperative sequelae, 90.4% of patients in our study were classified as Visick grade I or II. Excluding the 2 patients with recurrent ulcers, 7 of 83 patients (8.4%) were Visick grade III or IV. One patient had severe dumping (Visick IV) and the other six patients had Visick III dumping or diarrhea. The retrospective nature of this study may well have underestimated the Visick scores, but it is doubtful that a telephone interview would have overlooked a grade III or IV post-gastrectomy complica-

tion. This is in agreement with the findings of Herrington, Sawyers and Scott[17] that 94% of the patients had excellent to good follow-up results, with 1% having severe diarrhea and no severe symptoms of dumping. The Mayo Clinic study[16] with a follow-up of 290 patients had a grade IV incidence of diarrhea and dumping of 1.0% and 0.7% respectively. In 542 patients followed up by Palumbo and Sharpe,[15] moderate to severe diarrhea and dumping were found in 3.1% and 0.4% respectively. Vagotomy and antrectomy, therefore, has a small but important rate of serious postoperative adverse effects. Highly selective vagotomy is, however, not without side-effects. In the study reported by Hoffmann, Olesen and Jensen,[7] excluding the 32 patients with recurrent ulcers who were placed in Visick IV, 10.7% of patients had grade IV symptoms consisting mostly of dyspepsia with dumping or dyspepsia alone; none of the patients had grade IV diarrhea. Jordan and Thornby[1] and Donahue and associates,[2] similarly, reported no severe diarrhea in their patients, but 5% of patients in Donahue's series had either severe dysphagia or dumping. From these three studies totalling 375 patients, it is apparent that severe diarrhea is extremely uncommon following highly selective vagotomy, but there is still a low incidence of significant dumping. Review of four randomized studies comparing highly selective vagotomy with vagotomy and antrectomy[1,2,5,6] revealed consistently better results with highly selective vagotomy with a greater percentage of patients in Visick grades I and II. Nevertheless, a small but important number of patients did experience grade IV complications after both operations.

Hoffmann and colleagues[19] recently completed a prospective randomized trial comparing truncal, selective and highly selective vagotomy in the elective treatment of duodenal ulcer. The rate of ulcer recurrence after highly selective vagotomy (11- to 15-year follow-up) was 39.3%; this rate was not significantly different in any of the three groups. The rates of severe postvagotomy sequelae were similar in all groups, except for dumping, which was significantly less frequent following highly selective vagotomy. Taking into consideration medical and surgical treatment for ulcer recurrence, Hoffmann and associates concluded that none of these forms of vagotomy could be recommended as standard operative treatment for duodenal ulcer.

How should recurrent ulcers be managed? Those few occurring after vagotomy and antrectomy should first be treated with H_2-receptor antagonists, because the cholinergic and gastrin phases of acid secretion have already been interrupted. Those resistant to medical treatment will need a repeat vagotomy or gastric reresection, or both. Recurrent ulcers after highly selective vagotomy should also be managed medically first. Ten studies have been reviewed that address surgical management of ulcer recurrence after highly selective vagotomy.[1,3,6–13] A total of 76 (43.4%) of 175 recurrent ulcers were managed surgically, with the operation of choice being an antrectomy with or without a truncal vagotomy. In performing these procedures, there will undoubtedly be a risk of injury to the esophagus and also difficulty in mobilizing the lesser curvature of the stomach, with a possible increase in morbidity and mortality.

It is our opinion that the widespread use of H_2-receptor antagonists may lead to more refractory duodenal ulcers. Christensen, Bousfield and Christensen[20] and Bardhan and associates[21] have shown that the introduction of H_2-receptor antagonists has not altered the incidence of perforated and bleeding duodenal ulcers. No longer will intractability be the prime indication for operative intervention; obstruction and hemorrhage will assume increasing importance in the surgical management of duodenal ulcer disease. In this setting, highly selective vagotomy may have prohibitive recurrent ulcer rates, and a more definitive acid-reducing procedure may be needed.

Blackett and Johnston[12] stated "the incidence of recurrent ulceration after highly selective vagotomy is strongly influenced by the operating surgeon". This raises another issue, namely, the training of surgeons to perform near-perfect highly selective vagotomy. In the face of an absolute decrease in the surgical treatment of duodenal ulcer disease, adequate training of all prospective general surgeons may be very difficult.

Conclusions

Vagotomy and antrectomy offers acceptable mortality, morbidity and a relatively low incidence of Visick grade IV scores; its outstanding feature is the virtual freedom from recurrent ulceration over an extended period of follow-up that is operator-independent. Conversely, highly selective vagotomy has a slightly lower incidence of mortality and Visick IV scores but a significantly higher incidence of recurrent ulcers. These recurrent ulcers are operator-dependent and appear to increase with continued follow-up. Unfortunately, there is still no ideal operation for duodenal ulcer disease, and research should be directed toward a procedure that combines the advantages of both vagotomy and antrectomy and highly selective vagotomy. Until that time,

vagotomy and antrectomy should still remain in the surgeons' armamentarium for the management of duodenal ulcer disease.

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SESAP VI Question

Item 24

All of the following could be related to the genesis of peptic ulcer EXCEPT

(A) increased parietal cell mass

(B) increased sensitivity to gastrin

(C) elevated vagal tone

(D) reduced somatostatin

(E) elevated prostacyclin (PGI_2)

For the incomplete statement above select the best of the five completions.

For the critique of Item 24 see page 413

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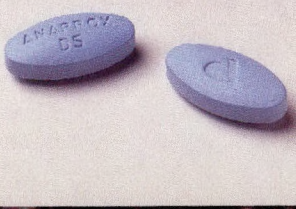

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SYNTEX®

1. Lundstrom V. Treatment of primary dysmenorrhea with prostaglandin synthetase inhibitors—A promising therapeutic alternative. Acta Obstet Gynecol Scand 1978; 57:421-428.

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Ductal Adenoma of the Breast

S.E. O'Brien, MD, FRCSC, FACS;* J.M. Kay, MD, FRCPC, FRCPath;†
Vicky S. Chen, MB, BS, FRCPC†

Ductal adenoma is a recently described benign tumour of the breast that can be mistaken for carcinoma in both frozen and paraffin sections. Such a case is presented. Fortunately a mastectomy was not performed, but the patient did undergo axillary node dissection. Surgeons and pathologists should familiarize themselves with this lesion so that patients do not have to undergo unnecessary mastectomies and axillary node dissections.

L'adénome canaliculaire est une tumeur bénigne décrite récemment qui peut être prise pour un carcinome, aussi bien dans les coupes en congélation qu'en bloc de paraffine. On décrit un tel cas. Heureusement, on n'avait pas eu recours à la mastectomie mais la patiente avait subi une dissection axillaire. Chirurgiens et pathologistes devraient se familiariser avec cette lésion afin d'éviter aux patientes une mastectomie et une dissection axillaire inutiles.

In 1984 Azzopardi and Salm[1] published details of 24 cases of a previously undescribed benign breast tumour which they named "ductal adenoma". Three of the cases were derived from their own institution, and 21 were seen in patients referred for consultation. It is important to recognize this tumour because it may mimic carcinoma. In some of the cases reviewed by Azzopardi and Salm, the patient had been subjected to mastectomy because of an erroneous diagnosis of malignancy made usually, but not exclusively, on frozen-section examination. Only one further case has been reported in the pathology literature.[2] Since it is important that both surgeons and pathologists be aware of this lesion we describe the clinical and pathological features of a further case.

Case Report

A 63-year-old woman was discovered to have a mass in her right breast during a routine physical examination carried out by her family physician. She had not noted a nipple discharge. Twenty-nine years previously she had undergone a biopsy of the left breast for benign fibrocystic disease. Eighteen years previously she had received radiotherapy for carcinoma of the cervix with no recurrence to date. Physical examination revealed a firm, irregular, nontender mass in the upper quadrant of the right breast, measuring approximately 2 cm in diameter. It was not attached to the overlying skin or underlying pectoral muscles. There was slight retraction of the nipple which the patient stated had been present for many years. No lymph nodes were palpable in the axilla. The left breast and axilla were normal.

Bilateral xeromammograms (Fig. 1) demonstrated a fairly smooth, marginated lesion (2 cm in diameter) in the 12 o'clock position of the right breast with no associated calcification. The radiologist felt this

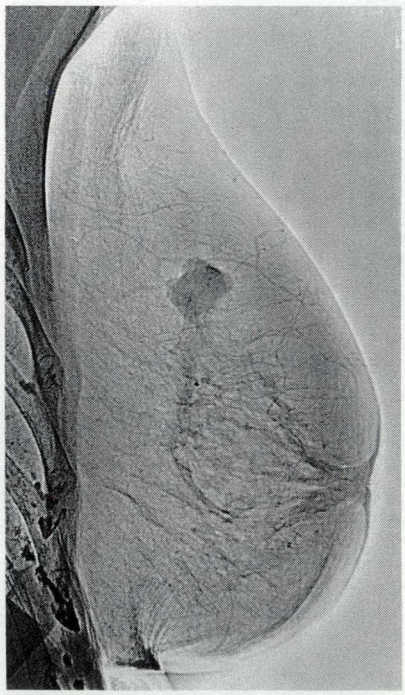

FIG. 1. Xeromammogram showing fairly smooth, noncalcified, marginated lesion with partial halo. Nipple is retracted.

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lesion was probably benign, representing a fibroadenoma or cyst. Fine-needle aspiration of the mass yielded no fluid. Cytologic examination (Fig. 2) revealed a cellular aspirate consisting of slightly overlapping sheets of epithelial cells with occasional dissociated ones. Some nuclei had one or multiple nucleoli. The cytologic findings were interpreted as "suspicious for malignancy".

The patient was advised that the lesion was probably malignant. Treatment options were discussed and she elected to undergo a segmental mastectomy and axillary dissection if the malignant nature was confirmed by frozen section. A preoperative chest film showed no evidence of metastatic disease. At surgery, a wide excision of the mass was carried out with a good margin of surrounding normal breast tissue. Grossly, the lesion was well circumscribed, homogeneous, greyish and suggestive of a medullary carcinoma. A frozen section was reported as carcinoma. Axillary lymph-node dissection was then performed using a separate incision. The postoperative course was uncomplicated.

Pathological Findings

The specimen consisted of an oval mass of adipose tissue (6 × 5 × 4 cm). In the centre of the tissue was a well-circumscribed oval nodule of firm, grey tissue measuring 2 × 1.5 × 1.5 cm. Microscopic examination showed a lobulated adenomatous lesion surrounded by dense hyalinized collagen with some elastic tissue consistent with the wall of a distended duct. In the centre of the nodule was a stellate fibrous scar (Fig. 3). The nodule was composed of glandular tubules made up of two cell types, epithelial and myoepithelial (Fig. 4). A small proportion of the epithelial cells showed apical snouts. The glandular tubules were small. Most were empty, but some contained eosinophilic secretion. Occasional tubules contained small circular foci of calcification. Most of the tubules were round, but some were elongated and branching. The epithelial tubules were supported by a sparse collagenous stroma with scanty elastic fibrils. The epithelial cells showed no significant pleomorphism or hyperchromatism. Mitotic figures were rare and morphologically normal. In some areas, the fibrous tissue surrounding the adenomatous nodule was attenuated, and glandular tissue was protruding into the duct wall. In some microscopic fields glandular tissue appeared to be entrapped within the wall of the duct simulating an invasive malignant lesion. The lesion was diagnosed as ductal adenoma of the breast. The sections were referred to J.G. Azzopardi who confirmed the diagnosis. The axillary

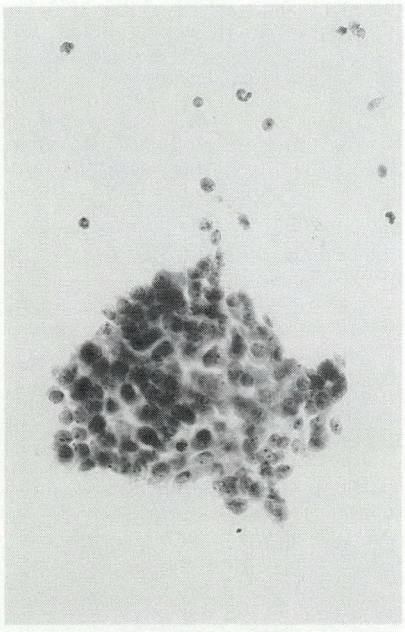

FIG. 2. Fine-needle aspirate. Slightly overlapping sheets of epithelial cells with occasional dissociated cells at top. Most nuclei include one or two nucleoli (Papanicolaou stain, original magnification × 500).

FIG. 3. Ductal adenoma of breast. Lesion is lobulated and surrounded by dense hyalinized collagen consistent with wall of distended duct (arrow). There is central pale, stellate fibrous scar (s) (hematoxylin and eosin, original magnification × 7).

FIG.4. Ductal adenoma of breast. Glandular tubules composed of epithelial and myoepithelial cells in collagenous stroma. At top glandular tissue extends into wall of duct simulating invasive malignant lesion (hematoxylin and eosin, original magnification × 200).

dissection included five small benign lymph nodes.

Discussion

Twenty-five cases of ductal adenoma of the breast have been described in the literature.[1,2] We present an additional case. All the patients in the literature were women ranging in age from 26 to 76 years (mean 52 years). Twenty of the 25 patients were older than 40 years. All had presented with a palpable breast lump that had been present for periods ranging from several weeks to several years. All lesions were unilateral. Eleven tumours were discrete solitary nodules, 14 were multiple. In the patients with multiple nodules, most of the tumours formed compact aggregates, but in some cases they were separated by up to 1 cm. The multiple nodules mostly appeared to involve different parts of the same duct system. The lesions varied from 0.5 and 3 cm in maximum diameter.

Clinically and radiologically ductal adenoma can simulate a malignant lesion because of its occurrence in older patients, the hardness and irregularity of many lesions and the frequency of microcalcification. Cytologically, a cellular aspirate and the presence of nucleoli indicate a proliferative lesion. In older women these features tend to raise concern for malignancy. The relative cohesiveness of the cells and the absence of definite malignant nuclear criteria are helpful hints that the lesion may be benign. Fibrous sclerosis with resulting distortion of the glandular elements and entrapment of glandular elements within the wall of the duct may simulate carcinoma in both frozen and paraffin sections. Recognition that the lesion is composed of both epithelial and myoepithelial cells is the most reliable criterion in identifying this lesion as benign. Unfortunately, the quality of frozen sections is such that it is not always possible to recognize such subtle features of cellular differentiation.

Ductal adenoma constitutes the third major type of adenoma in the breast, in addition to the already widely recognized nipple adenoma and tubular adenoma. Ductal adenomas differ from duct papillomas in that the latter occur in the major ducts under the areola and are usually associated with nipple discharge. Duct papillomas are tiny and rarely palpable. They have an arborescent fronded structure. Ductal adenomas on the other hand seem to occur in the more peripheral ducts. They are palpable and solid and they do not present with nipple discharge. On morphologic grounds, Azzopardi and Salm[1] considered that ductal adenoma arose from medium-sized and small ducts but not major areolar ducts. Gusterson and colleagues[2] carried out immunocytochemical studies in one case and found that the cells making up the lesion carried the phenotype of cells derived from a terminal ductal lobular unit, rather than those of a larger duct.

Our patient was fortunate in that a mastectomy was not performed, although she did have unnecessary dissection of the axillary nodes. Recognition of this lesion by both surgeons and pathologists could prevent unnecessary mastectomies and axillary node dissection.

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This list is an acknowledgement of books received. It does not preclude review at a later date.

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Inflammatory Bowel Diseases 1990. Edited by D. Rachmilewitz and J. Zimmerman. Vol. 11 of Developments in Gastroenterology. 277 pp. Illust. Kluwer Academic Publishers, Boston. 1990. $97.50 (US). ISBN 0-7923-0657-0

Medicine, Sport and the Law. Edited by Simon D.W. Payne. 381 pp. Illust. Blackwell Scientific Publications, Oxford; C.V. Mosby Co., Scarborough, Ont. 1990. Price not stated. ISBN 0-632-024439-9

Multiple Choice Questions for the MRCP. 2nd ed. Pankaj Joshi. 245 pp. Butterworth & Co. (Publishers) Ltd., London. 1990. $29.95 (US). ISBN 0-407-00551-X

Spinal Surgery: Science and Practice. Edited by Robert A. Dickson. 560 pp. Illust. Butterworth & Co. (Publishers) Ltd., London. 1990. $175 (US). ISBN 0-407-01791-7

Surgical Endocrinology: Clinical Syndromes. 2nd ed. Edited by Stanley R. Friesen and Norman W. Thompson. 474 pp. Illust. J.B. Lippincott Co., Philadelphia. 1990. $79.50 (US). ISBN 0-397-50861-1

Surgical Pathology of the Breast. K. Rogers and A.J. Coup. 149 pp. Illust. Wright/Butterworth & Co. (Publishers) Ltd., London. 1990. $87 (US). ISBN 0-7236-0965-9

Textbook of Liver and Biliary Surgery. William C. Meyers and R. Scott Jones. 489 pp. Illust. J.B. Lippincott Co., Philadelphia. 1990. $99.50 (US). ISBN 0-397-50774-7

Thoracic Surgical Techniques. F.C. Wells and B.B. Milstein. 280 pp. Illust. Baillière Tindall Ltd./W.B. Saunders Company, London; HBJ-Holt-Saunders Distribution Services, Toronto. 1990. $201.50. ISBN 0-7020-1239-4

Antibiotic Handbook and Pre-printed Perioperative Order Forms for Surgical Antibiotic Prophylaxis: Do They Work?

M.J. Girotti, BSc, MD, FRCSC; S. Fodoruk, BScPharm;* J. Irvine-Meek, BSc, PharmD;† O.D. Rotstein, MD, MSc, FRCSC

The authors attempted to compare the value of two strategies — an educational (antibiotic handbook) and a control (perioperative pre-printed physician order form, which contained antibiotic orders) — in modifying physicians' patterns of antibiotic prophylaxis for preventing infection in patients who undergo elective surgery. They reviewed the charts of 240 such patients on five different surgical services in one teaching hospital. Use of the antibiotic handbook (educational strategy) increased overall compliance with the recommended regimens from 11% to 18% ($p = 0.06$). The control strategy (perioperative pre-printed physician order form) increased compliance from 17% to 78% ($p < 0.01$).

Les auteurs ont tenté de comparer le succès de deux stratégies — pédagogique (à l'aide d'un livre de référence sur les antibiotiques) ou dirigée (avec un feuillet d'ordonnance préimprimé renfermant des instructions sur les antibiothérapies peropératoires) — visant à modifier les habitudes des médecins dans leur choix d'une antibiothérapie préventive pour les patients devant subir une chirurgie non urgente. Ils ont passé en revue les dossiers de 240 patients des cinq différents services chirurgicaux d'un hôpital universitaire. L'emploi du livre de référence sur les antibiotiques (l'approche pédagogique) a fait passé le taux de conformité aux traitements recommandés de 11% à 18% ($p = 0.06$). L'approche dirigée (le feuillet d'ordonnance préimprimé) a amélioré le taux de conformité de 17% à 78% ($p < 0.01$).

Antimicrobial use has increased markedly since the early 1970s and currently accounts for up to 25% of the total drug inventory of major hospitals. In the United States and Canada, it is believed that almost 20% of all dollars spent on ethical drug products are for antibiotics.[1,2] The recognized benefit and expanded use of antibiotics for both prevention and treatment of postoperative sepsis have contributed substantially to this escalation in drug use.[2,3] Well-designed clinical trials have demonstrated the clinical benefit of perioperative prophylactic antibiotic regimens with both elective and emergency surgery.[4,5] However, for perioperative antimicrobial prophylaxis to be clinically effective, several principles for its use must be adhered to. The antimicrobial agent must be present in high tissue concentrations during the operative procedure and should be discontinued in the early postoperative period.

Continued pressure on the health care system to provide both efficacious and cost-effective patient care has resulted in the introduction of various strategies into hospital-based medical practice aimed at modifying physicians' patterns of drug usage. To this end, our hospital established an Antibiotic Committee which reports directly to the Pharmacy and Therapeutics Committee.[6] The representatives to this committee were chosen from the major clinical departments, hospital administration, pharmacy and the medical/surgical housestaff. This Antibiotic Committee assumed responsibility for both the formulary control of all antimicrobial agents and surveillance of antimicrobial usage. Several strategies (e.g., restricted drug list, limited microbial sensitivity reporting, periodic pharmacy bulletins) had been tried but had failed to improve the pattern of use of antibiotics for surgical pro-

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phylaxis. In 1987, a pocket size "antibiotic handbook", based on recently published clinical trials, was developed by this committee in an effort to modify the perioperative pattern of physician drug use. This handbook recommended guidelines for antimicrobial prophylaxis in the area of surgical wound infection. During the development and institution of these guidelines, a single surgical service decided to incorporate these guidelines for surgical procedure prophylaxis into a comprehensive pre-printed perioperative physician order form. A similar system had been in use on another surgical service for over 1 year. Employing a chart review in a before-and-after study design on selected surgical services, we compared the impact of an educational strategy (the antibiotic handbook) and a control strategy (pre-printed physician order form) designed to modify physician prescribing habits in elective surgical prophylaxis.

Methods

The study was conducted on five selected surgical services (A to E) of the Toronto General Hospital, a 1000-bed teaching hospital with more than 100 attending surgeons and 175 surgical housestaff (interns, residents and fellows). Most (more than 95%) antibiotic orders are written by the surgical housestaff. The information concerning surgical antibiotic prophylaxis and contained within the antibiotic handbook and on the pre-printed physician order forms was based on a literature review and input from the individual surgical divisions.

The handbook, which also contained general educational material on infectious disease, was distributed to attending surgical staff and housestaff with a covering letter from the Antibiotic Committee, indicating that the recommendations contained in the handbook were to be followed for the perioperative use of antimicrobial agents. The impact of the handbook on antimicrobial use was examined on services A, B and C, and the effect of the pre-printed physician order form was investigated on services D and E. Service D had been using such a form for over 1 year before this review. Service E introduced the pre-printed perioperative order form at approximately the same time as the antibiotic handbook was circulated. The pre-printed order forms did offer the physician limited options when ordering perioperative antimicrobial agents.

The study design was of a before-and-after chart review. The first review occurred 1 year before the introduction of the antibiotic handbook or the pre-printed physician order form on service E. For each surgical service studied, a list of possible study patients was generated from consecutive daily operative lists. A period of 4 weeks was chosen within which case records were examined for possible inclusion in the study. In a similar fashion, a second review occurred 6 months after distribution of the handbook or order form so as to accumulate an identical number of patient case records for review within each surgical service.

A patient was included in the study if the chart indicated the performance of a selected elective surgical procedure for which prophylaxis guidelines were outlined in the antibiotic handbook. Antibiotic usage was considered to be therapeutic and the patient was therefore excluded from the study when the chart indicated any of the following: antibiotic treatment of an intercurrent infection within the week preceding surgery; a major intraoperative problem which converted the procedure to a contaminated one; prophylaxis for bacterial endocarditis.

The prophylactic antibiotic regimen recommended in the antibiotic handbook or the pre-printed physician order form was compared with the patient medication records and the intraoperative anesthesia records of the patients selected for study. The prophylactic antibiotic regimen prescribed was analysed for antibiotic choice, dosage, route, frequency of ordered drug administration, necessity of intraoperative antibiotic dosing and, finally, duration of use. A prophylactic antibiotic regimen was considered appropriate (i.e., no drug error) if all of the above, excluding actual time of administration of first dose (a nursing-dependent factor) corresponded to the recommendations. The rate of appropriate usage for the individual surgical services was calculated. Differences between study periods for the antibiotic handbook and the pre-printed physician order form were compared using χ^2 analysis. The results were further analysed to identify specific components of the antibiotic orders that were contrary to the recommendations for surgical prophylaxis. Dollar costs or adverse reactions of the prophylactic antibiotic regimens were not addressed.

Results

A total of 230 patient charts were reviewed. For the statistical evaluation, services A, B and C (antibiotic handbook) were collectively analysed, but services D and E were examined both as single services and as a combined second group. For services A, B and C, overall compliance increased from 11% to 18% ($p = 0.06$) after the introduction of the antibiotic handbook. On service D, which had been using a pre-printed physician order form

previously, overall compliance did not improve significantly during the study period. After the introduction of the pre-printed physician order form, service E experienced a significant increase in compliance rate from 17% to 78% ($p < 0.001$). The overall compliance rate for the combined services D and E following the introduction of the pre-printed physician order form was 84%.

Specific practices of antimicrobial prophylactic drug prescribing are detailed in Table I. Before the introduction of the antibiotic handbook on services A, B and C, the choice of antimicrobial agent and the timing of drug administration (duration and frequency) were the most commonly observed drug errors. The introduction of the antibiotic handbook did not improve these aspects of drug use. Service D, which had been using a pre-printed physician order form, reduced the wrong-frequency drug errors after the circulation of the antibiotic handbook and a re-emphasis of the pre-printed order forms. Service E significantly reduced observed drug errors with respect to frequency and duration after the introduction of the pre-printed physician order forms.

A comparison of the control or educational strategies for modifying physician prescribing habits in the perioperative use of antimicrobial agents indicates that the pre-printed physician order form containing an antibiotic component was better than the antibiotic handbook (overall compliance rate of 84% versus 18% after the introduction of the strategy, $p < 0.001$).

Table I. Specific Drug Error Rates Observed on Individual Surgical Services*

	Surgical service			
Drug error	A + B + C (n = 166)	D (n = 40)	E (n = 24)	D + E (n = 64)
Wrong drug	55/51	0/0	8/0	3/0
Wrong dose	17/13	0/0	8/8	3/3
Wrong frequency	22/18	20/5†	64/8†	36/6
Wrong duration (too long)	31/28	0/0	40/16†	16/6†
Intraoperative dose	11/6	0/0	0/8	0/3

*Numbers indicate % before/% after.
†$p < 0.05$ by χ^2 analysis, before versus after.

Table II. Comparison of Drug Utilization Strategies

Method	Series	Impact
Educational		
Weekly lectures, CME courses, bulletins, newsletters	2,9,10	Minimal positive effects, failed to control costs
Pharmaceutical detailing	2,11	No data available, obvious company bias
Academic detailing	12,13	Short- and long-term positive impact on use and costs
Peer review	14–16	Educational component high, resource intensive, positive impact on use
Handbook	17	Short-term benefit only
Control		
Controlled formulary	18	Reduced cost and inventories
Selective reporting of sensitivity testing	18	No data available
Automatic stop order policy	2,18	Effective control for prophylaxis and empiric therapy
Mandatory consultation (service or MD)	2,19,20	Reduced costs, improved drug use
Antibiotic order form	21–23	Reduced drug errors and drug costs

Discussion

On the basis of internal reviews such as ours, the majority of clinical and pharmacy departments have adopted drug utilization programs which have resulted in the introduction of various strategies in an attempt to modify physician prescribing habits.[7] These attempts can be generally classified as either educational or control strategies.[8] Examples of educational mechanisms include pharmacy bulletins and newsletters, lectures and conferences, peer review of drug usage, handbooks (such as the antibiotic handbook) and pharmaceutical or academic drug detailing. Control strategies include direct formulary control, mandatory consultation with infectious disease experts or clinical pharmacists, pre-printed antibiotic order forms, automatic antibiotic stop orders and controlled antibiotic sensitivity reporting from the microbiology laboratory. These measures of antibiotic control have not been evaluated rigorously until recently. Table II[2,9–23] summarizes the results of these studies. Few reports specifically address the issue of controlling antibiotic use in the perioperative prophylaxis of elective surgical procedures. The present study investigates the efficacy of two of these strategies in this setting. Our results indicate that the introduction of a purely educational strategy in the form of an antibiotic handbook provided only a marginal improvement in the overall compliance with our recommendations on three surgical services. However, the introduction of a control strategy through the use of a pre-printed physician order form in the perioperative period resulted in a dramatic improvement in compliance with the recommended antibiotic regimens. Employing a similar handbook, D'Eramo and colleagues[17] reported a short-term im-

provement (less than 3 months) when the handbook was introduced into a hospital setting in an attempt to modify the patterns of physician drug use for empiric therapy.

The single most impressive educational strategy affecting physician drug use appears to be "academic detailing", which is a labour-intensive program of ongoing one-to-one pharmacist to physician counselling. This mechanism has been demonstrated to influence physician prescribing patterns both in the short- and long-term assessment of drug utilization.[12,13] In this regard, our study could be criticized for the omission of a program of regular reminders from the clinical and pharmacy attending staff to the physicians most often prescribing perioperative antimicrobial agents that the antibiotic handbook recommendations must be adhered to. This is a key element in any educational strategy.[2]

Several recent, well-designed studies have addressed the use of specialized pre-written antibiotic order forms, which provide the physician with clear choices and directions for either prophylaxis, empiric or directed therapy, as well as automatic antibiotic stop orders. Such programs effectively reduced drug errors, lowered drug-dollar costs and were not perceived as interfering with patient care or educational objectives in teaching hospitals.[21-23] The results of this study indicate that the use of a pre-printed perioperative physician order form is an effective method for modifying physician behaviour in prescribing perioperative antimicrobial prophylaxis. We believe that such a control strategy should be part of a coordinated antimicrobial utilization program combining both educational and control mechanisms and overseen by an antibiotic committee with multidisciplinary hospital representation.

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Correction

In the June 1990 issue of the journal, there was an omission in the article "Post-traumatic microvascular reconstruction: Toronto's 500th reattachment" by D.P. Ewart and R.M. Zuker (pages 239 to 242). On page 239, second column, the name of Dr. Brian Boyd should be added to the listing of Toronto's microvascular team. The journal and the authors apologize to Dr. Boyd for this omission.

Factors Influencing the Effectiveness of Extracorporeal Shock-Wave Lithotripsy of Biliary Duct Calculi

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The authors examined the effectiveness of extracorporeal shock-wave lithotripsy on patients who had bile-duct stones. Thirty-eight patients were treated with an unmodified HM-3 Dornier lithotripter; 35 (92%) patients either passed the stone fragments spontaneously or had them reduced to a size which allowed removal by percutaneous or endoscopic techniques.

As stone size increased so did the number of shocks required for satisfactory fragmentation, the number of treatments and the rate of post-treatment manipulation.

The number of stones was not as important a variable as the authors expected. Pre-treatment sphincterotomy was not always necessary and was of no benefit in terms of spontaneous passage of fragments. Complications were minor. Extracorporeal shock-wave lithotripsy of stones throughout the biliary tree is a safe, effective and invaluable adjunct in the managment of bile-duct stones.

Les auteurs ont étudié l'efficacité de la lithotripsie par ondes de choc chez des patients qui souffraient de calculs biliaires. Trente-huit patients on été traités à l'aide d'un lithotritreur HM-3 Dornier non modifié; 35 patients (92%) ont, soit passé les fragments calculeux de façon spontanée, ou leur taille fut réduite suffisammnent pour qu'ils puissent être retirés par des techniques percutanées ou endoscopiques.

Avec la taille des calculs, ont augmenté le nombre de chocs requis pour obtenir une fragmentation satisfaisante, le nombre de traitements et le taux de manipulations post-thérapeutiques.

Le nombre de calculs n'a pas représenté une variable aussi importante que les auteurs l'avaient anticipé. Une sphinctérotomie préthérapeutique n'a pas toujours été nécessaire et n'a aucunement contribué au passage spontané des fragments. Les complications ont été bénignes. La lithotripsie extracorporelle par ondes de choc des calculs dans tout l'arbre biliaire est un adjuvant sûr, efficace et important du traitement des calculs biliaires.

Extracorporeal shock-wave lithotripsy (ESWL) has revolutionized the management of upper urinary tract stones. Because of its success and safety, there has been much interest in expanding its indications. Many centres have developed programs for the lithotripsy of gallbladder stones. These calculi can be satisfactorily broken up, but there remain questions about the fate of residual fragments and long-term recurrence rates.[1-3] A more clear-cut indication for this treatment is in the management of biliary duct calculi.[4,5] Although these are often amenable to basket extraction through matured T-tube tracts, percutaneous transhepatic tracts and endoscopically placed catheters following endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy, there remains a group of patients in whom these techniques fail, are technically impossible or are unduly hazardous.[4] In these patients ESWL has been an important adjunct to solving many of these complex problems and avoiding further open surgery.[5]

During our experience with ESWL of biliary duct calculi, it has become apparent that several factors related to calculi and anatomy influence the effectiveness of the therapy. This paper reviews these issues.

Patients and Methods

Over a 2-year period, 38 patients (16 men, 22 women) with residual or *de novo* gallstones in the cystic (4 patients), hepatic (7) or common bile ducts (32) were treated using an unmodified HM-3 Dornier lithotripter (Dornier Medical Systems, Marietta, Ga.). (Five patients had stones in more than one duct.) The patients ranged in age from 23 to

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92 years (mean 63 years, median 68 years).

All patients were initially operated upon or assessed by a general surgeon and subsequently by an interventional radiologist. The time from open biliary surgery to ESWL in 36 patients ranged from 8 days to 22 years (mean 4.8 years, median 2 months). All stones were considered inappropriate for percutaneous or endoscopic manipulation because they were too large or the patient had an anatomical abnormality (e.g., duodenal diverticulum) (15 patients), because the patient had undergone unsuccessful attempts at such procedures (12) or because the stones were impacted postoperatively (11). Stone size was measured as the greatest diameter of the largest stone and varied from 2 to 35 mm (mean 16 mm); one was opaque and the remainder were lucent. Sixteen patients had multiple stones. Either epidural (33) or general (5) anesthesia was used for all patients. Imaging was made possible by introducing dye through a cholecystostomy (2 patients) or transhepatic (8), nasobiliary (11) or T tubes (17). All patients were positioned supine initially, but it was necessary to reposition some (14 patients) prone for satisfactory visualization.

Twenty-six patients were treated once, 11 twice and 1 three times.

The average number of shocks required for satisfactory fragmentation was 2995 (range 575 to 8000 shocks) at 18 to 25 kV. The maximum number of shocks used during one session was 3200. The influence on treatment of stone size, multiplicity and location are shown in Tables I to III. Tube cholangiograms were obtained 24 hours after ESWL and later when necessary to assess stone fragmentation and clearance.

Table I. Influence of Size of Stones on Treatment

	Stone size, mm		
Treatment	**1–10 (n = 10)**	**11–20 (n = 23)**	**21–30 (n = 5)**
Mean no. of shocks	1720	3246	4590
No. of treatments			
1	10	14	2
2	0	9	2
3	0	0	1

Table II. Influence of Number of Stones on Size and Treatment

Size/treatment	**Single (n = 22)**	**Multiple (n = 16)**
Mean size, mm	15	14
Mean no. of shocks	3104	2845
No. of treatments		
1	13	13
2	8	3
3	1	0

Table III. Influence of Ductal Location of Stones on Treatment

	Duct		
Treatment	**Common bile (n = 32)**	**Hepatic (n = 7)**	**Cystic (n = 4)**
Mean no. of shocks	2720	1882	2900
No. of treatments			
1	24	6	3
2	7	1	1
3	1	0	0

Results

Of the 38 patients, 35 (92%) either passed the fragments spontaneously (25) or had them reduced to a size which could be removed by percutaneous or endoscopic techniques (10) (Table IV). Two patients subsequently underwent open surgery. One was found to have a

Table IV. Variables Influencing the Effectiveness of Extracorporeal Shock-Wave Lithotripsy (ESWL)

		Size, mm			Number		Sphincterotomy	
Variable	**Overall, no. (%)**	**1–10 no. (%)**	**11–20 no. (%)**	**21–35 no. (%)**	**Single no. (%)**	**Multiple no. (%)**	**No no. (%)**	**Yes no. (%)**
No. of patients	38	10	23	5	22	16	26	12
Spontaneous passage of fragments	25(66)	8(80)	15(65)	2(40)	15(68)	10(62)	17(65)	8(67)
at 24 h	14(37)	5(50)	8(35)	1(20)	9(41)	5(31)	10(38)	4(33)
at 1 mo	11(29)	3(30)	7(30)	1(20)	6(27)	5(31)	7(27)	4(33)
Extraction of residual fragments	10(26)	1(10)	7(30)	2(40)	7(32)	3(19)	8(31)	2(17)
Post-SWL	2(5)	1(10)	0(0)	1(20)	0(0)	2(13)	0(0)	2(17)
Unknown	1(3)	0(0)	1(4)	0(0)	0(0)	1(6)	1(4)	0(0)

common-bile-duct tumour, which precluded passage of stone fragments and the other was an elderly man who had a large (35 × 20 mm) common-bile-duct stone, which did not fragment well on a single treatment, and who refused repeat ESWL. Another man's T tube fell out after the ESWL, and follow-up cholangiography was not possible; he remained asymptomatic.

Patients with smaller stones passed the fragments more frequently and earlier and required fewer manipulations after ESWL than those with larger stones (Table IV). Single stones passed more frequently and earlier than multiple stones. Extraction of residual fragments was required after ESWL for more single than multiple stones, but both patients requiring an open common-duct exploration for definitive therapy had multiple stones (Table IV).

Sphincterotomy did not improve spontaneous clearance rates or reduce the likelihood of subsequent open surgery but it did decrease the rate of post-treatment manipulations (Table IV).

Spontaneous passage (66% to 75%) and post-treatment manipulation (25% to 29%) rates were similar for all three parts of the biliary tree. Stones from the hepatic ducts seemed to clear slower than those from the common bile and cystic ducts (Table V).

In the 11 patients with impacted stones postoperatively and immature T-tube tracts, the stones all cleared spontaneously after ESWL — 5 within 24 hours and 6 within 1 month.

Extracorporeal shock-wave lithotripsy was well tolerated and the majority of complications were minor (Table VI). There was no correlation between complications and the stone size, number or location or the presence of sphincterotomy, with the exception of post-treatment diarrhea — 90% of patients in this group had undergone spincterotomy. Cardiac arrest occurred 2 hours after ESWL in a man with known cardiac disease who had suffered a myocardial infarction 5 months previously. He was successfully resuscitated.

Discussion

Until recently, retained biliary tract calculi have been removed either endoscopically or by percutaneous basket extraction. The latter requires a 5- to 7-week waiting period for maturation of the T-tube tract. When these techniques failed or were impossible, further open biliary surgery was often required. Our series offers a new approach and confirms that ESWL can be a safe and an effective adjunct in the management of these stones.[5,6] An impressive overall success (stone free) rate was achieved in 92% of patients. In two-thirds of the group no further intervention was required after ESWL. This is particularly important for the elderly patients treated, many of whom had a variety of other major medical problems. It is evident that stone burden is an important variable influencing treatment and success. As stone size increases, so does the number of shocks required for satisfactory fragmentation, the number of required ESWLs and the rate of post-treatment manipulations.

Multiplicity of stones was not as important a variable as expected since it was associated with only a slightly decreased spontaneous passage rate and a similar rate of post-treatment intervention (extraction or surgery) as compared with single stones. In most cases of multiple stones there was a single obstructing calculus at the bottom of a column of stones, and when it was successfully treated, passage of or access to the remainder were possible.

In this series our experience with different stone compositions was limited, but the one calcified stone fragmented and cleared extremely well.

Although it has been implied previously that sphincterotomy is necessary before ESWL in all these patients,[6] it is clear that this is not required and that many patients can be treated successfully without the risk of undergoing routine ERCP and endoscopic papillotomy before ESWL. In fact, this procedure did not offer any benefit in terms of spontaneous passage of fragments.

Although there were some initial concerns, it is clear that stones throughout the biliary tree, including the intrahepatic ducts, can be

Table V. Influence of Ductal Location on Effectiveness of Extracorporeal Shock-Wave Lithotripsy

Variable	Duct, no. (%)		
	Common bile (n = 32)	Hepatic (n = 7)	Cystic (n = 4)
Spontaneous passage of fragments	21(66)	5(71)	3(75)
at 24 h	14(44)	2(29)	2(50)
at 1 mo	7(22)	3(43)	1(25)
Extraction of residual fragments	8(25)	2(29)	1(25)
Post-ESWL	2(6)	0(0)	0(0)
Unknown	1(3)	0(0)	0(0)

Table VI. Complications Occurring After Extracorporeal Shock-Wave Lithotripsy

Complication	No.
Elevated liver enzyme levels	31
Diarrhea	12
Sepsis	6
Hemobilia	3
Pancreatitis	1
Cardiac arrest	1

safely and effectively managed with ESWL.

Complications were minor. Although most patients had elevated liver enzyme levels after ESWL, these changes were transient. We are now pursuing further studies to determine whether there is any evidence of long-term hepatic dysfunction in this group. Postoperative diarrhea is secondary to the introduction of hypertonic contrast media during the visualization process. It usually resolves within 24 hours. More dye was required in patients with a sphincterotomy because of rapid transit into the duodenum and as a result most of the diarrhea occurred in this group. An attempt was made to reduce the severity of this by using half-strength dye and this seemed beneficial. The incidence of postoperative bacteremia and sepsis would likely be higher if tubes were not available for drainage and visualization. Antibiotics are now given routinely before ESWL and possibly will reduce the risk of this complication further. Although some controversy is likely to continue with respect to the usefulness of this treatment for gallbladder stones, it

is clear from our experience that extracorporeal shock-wave lithotripsy is a safe, effective and invaluable adjunct in the management of biliary duct calculi.

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Is Tube Repair of Aortic Aneurysm Followed by Aneurysmal Change in the Common Iliac Arteries?

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To address the concern that tube repair of an abdominal aortic aneurysm might be followed by aneurysmal change in the common iliac arteries, 23 patients who had undergone the operation were re-examined 3 to 5 years later. Although 9 had had minimal ectasia of these arteries preoperatively, in none of the 23 was there symptomatic or radiologic evidence of aneurysmal change on follow-up. Measurements of the maximum intraluminal diameters were made by computed tomography; they indicated no significant differences between the preoperative and follow-up sizes of the common iliac arteries. The variation in time to follow-up also showed no significant correlation with change in artery diameter.

Afin de vérifier si la réparation vasculaire d'un anévrisme de l'aorte abdominale est susceptible d'entraîner des altérations anévrismales des artères iliaques communes, 23 patients qui avaient subi cette opération ont été réexaminés de 3 à 5 ans plus tard. Même si 9 d'entre-eux présentaient, en préopératoire, une ectasie minime de ces artères, aucun des 23 n'a montré de symptômes ou de signe radiologiques d'altérations anévrismales à l'examen de contrôle. Des mesures des diamètres endoluminaux maximaux ont été faites par tomographie axiale; elles n'ont révélé aucune différence significative entre les diamètres préopératoires des artères iliaques communes et ceux qui ont été mesurés à l'examen de contrôle. Les variations dans le temps de suivi n'ont montré aucune corrélation significative avec les changements de diamètre artériel.

After the first reported repair of an abdominal aortic aneurysm by Dubost in 1952,[1] it was conventional teaching that such aneurysms should be repaired with a bifurcation graft to the common iliac arteries or, when the common iliac arteries were themselves aneurysmal or subject to severe atherosclerotic disease, by means of a graft to the common femoral arteries on each side, excluding the iliac arteries, which were usually oversewn or ligated. Recently, vascular surgeons have tended to use a tube prosthesis rather than a bifurcated one to repair aneurysms of the infrarenal abdominal aorta, the distal anastomosis being made to the aorta immediately above its bifurcation. However, no study has been carried out to investigate the subsequent fate of the common iliac arteries not repaired at the time of insertion of the tube prosthesis. It is not known, for example, whether the common iliac arteries dilate or develop aneurysmal change that may necessitate a second operation for correction. To this end, we studied patients who had minimal or no aneurysmal disease in the common iliac arteries at the time of tube repair of an aneurysm of the infrarenal abdominal aorta to investigate any change in size of the common iliac arteries over a 3- to 5-year period after repair of the original aneurysm.

Patients and Methods

Between 1981 and 1984, 205 abdominal aortic aneurysms were repaired by two surgeons; 87 of them were repaired by means of an aortobifemoral bypass, 15 by conventional bifurcation grafting to each common iliac artery and 103 by tube repair. Of the 103 patients treated by placement of a tube prosthesis, 18 had not undergone computed tomography before the operation. Only 83 of the 85 remaining patients could be contacted for follow-up, and 23 (28%) of them had died after discharge from hospital. This left 60 patients who were

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available for follow-up. Of these, 24 refused to return to the hospital for follow-up computed tomography for reasons such as age, sickness or distance from the hospital. Of the remaining 36 patients who were interviewed and had computed tomography, both pre- and postoperative computed tomography scans were available for only 23. Unfortunately, all scans obtained in 1981 were discarded, so the follow-up was reduced to a maximum of 5 years (3 years in 11 patients, 4 years in 9 and 5 years in 3).

The 36 patients who were available for follow-up were interviewed in July and August 1987 and questioned about symptoms that could have been associated with common iliac aneurysms. The 23 patients who had retrievable preoperative scans underwent non-contrast-enhanced computed tomography of the abdomen and pelvis in August 1987.

Before 1985, an EMI 5005 second-generation whole-body scanner (EMI, Northbrook, Ill.) was used. Follow-up scanning performed in this study in 1987 was carried out using the GE 9800 third-generation whole-body scanner (G.E. Medical Services, Milwaukee, Wisc.) which replaced the EMI 5005 in 1985. To correct for the discrepancy in scale that resulted from the use of two different scanners we measured the anteroposterior length of a designated vertebral body for a given patient on both preoperative and follow-up films. The ratio of the two measured lengths was then used to scale preoperative diameters to follow-up proportions. The margin scale on the GE 9800 scanner was then used to scale all measurements to actual size in centimetres. The difference in resolution and image quality between the second- and third-generation scanners is known.[2] Improved factors, such as increased matrix size from 256 × 256 to 512 × 512 (262, 144 pixels), reduced scanning time (from 20 to 2 seconds), and new resolution algorithm options allowed for much better visualization of the follow-up images. It was possible to make appropriate calculations, but the degree of error due to the difference between the two scanners was not quantifiable.

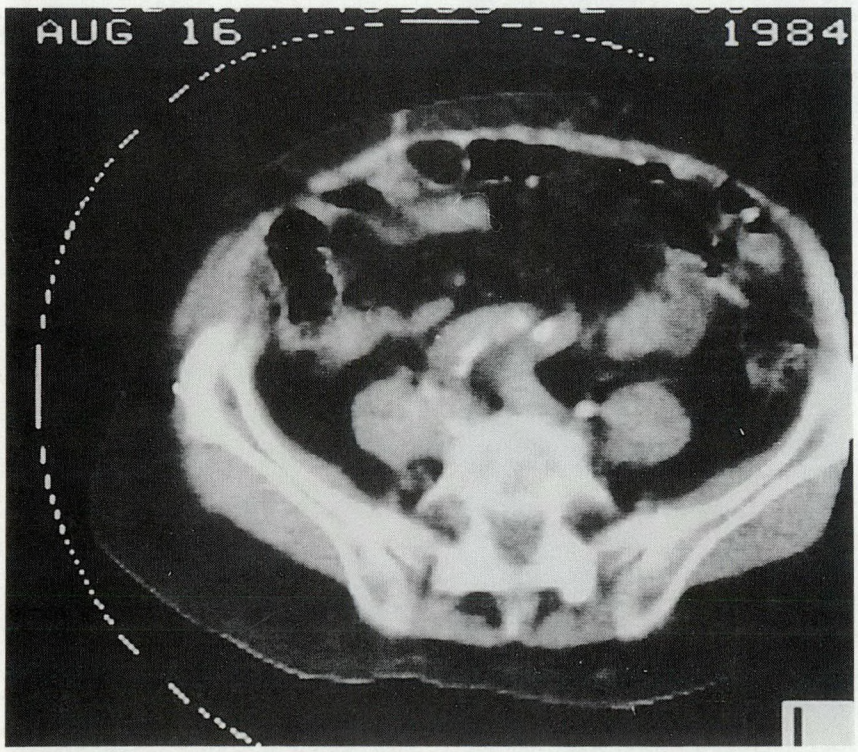

FIG. 1. Preoperative computed tomography scan of common iliac arteries.

Maximum common iliac artery diameters were obtained on both the preoperative (Fig. 1) and follow-up (Fig. 2) computed tomography scans, measured from intima to intima. These were intraluminal diameters which were easy to obtain despite the resolution difference between the two scanners. The right and left arteries were analysed separately because they were of different sizes preoperatively (1.4809 versus 1.2904 cm, $p > 0.025$).

The change in maximum diameter over a 3- to 5-year period for both right and left common iliac arteries was assessed for statistical significance. Differences between initial artery size or period of follow-up (3 versus 4 versus 5 years) and the change in maximum diameter of the common iliac arteries were analysed by analysis of variance. The mean of three measurements was obtained for each patient. Mean values for each group of diameters (right and left, preoperative and postoperative) were then calculated. The average standard error was 7%.

Results

Of the 36 patients interviewed, none had experienced symptoms, such as abdominal pain, that have been associated with common iliac artery aneurysms.[3-5] Of the 23 patients for whom both pre- and postoperative computed tomography scans were available, 14 (61%) had had no evidence of ectasia of the common iliac arteries before sur-

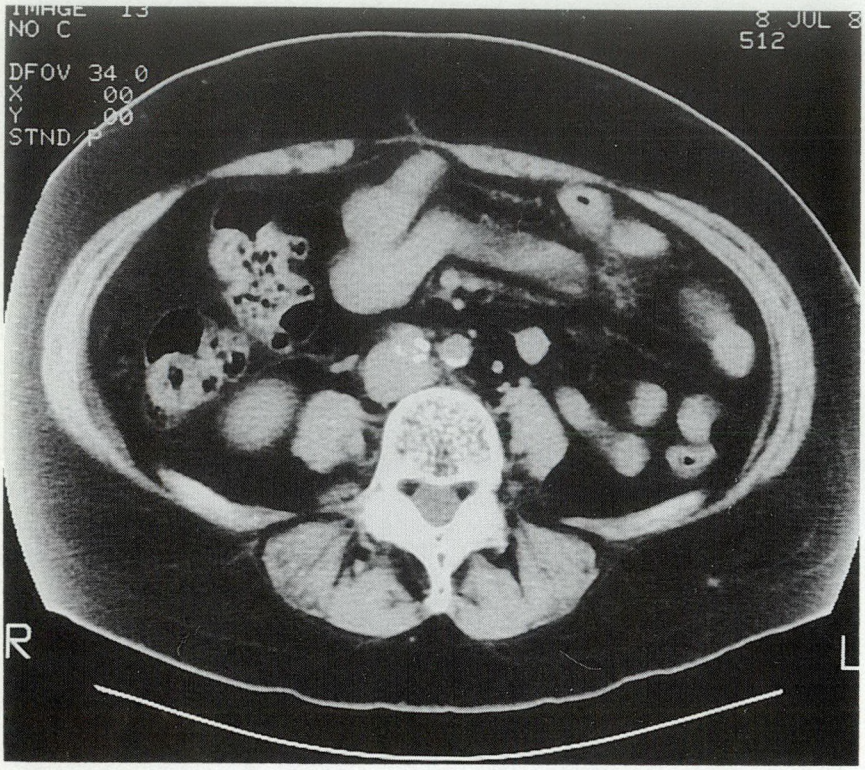

FIG. 2. Computed tomography scan of common iliac arteries at follow-up.

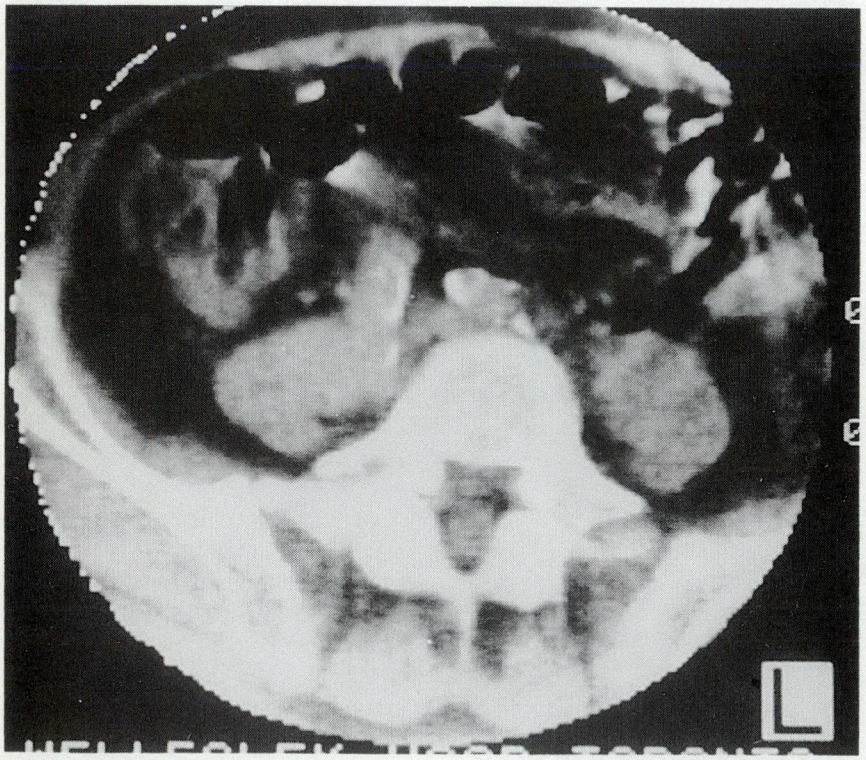

FIG. 3. Preoperative computed tomography scan showing ectasia of right common iliac artery.

gery, ectasia being defined as a generalized dilatation of a common iliac artery to more than 1.5 cm (but less than 3.0 cm) in diameter. The follow-up of these patients showed that they remained free of aneurysmal change in the common iliac arteries.

The remaining nine patients had had minimal ectasia (up to 3 cm in maximum diameter) preoperatively (Fig. 3) and on follow-up examination. None had had aneurysmal change greater than 3 cm.

Analysis indicated no significant change between the preoperative and follow-up maximum diameters for all 46 common iliac arteries. This was true both for the right (1.4089 versus 1.5204 cm) and left arteries (1.2904 versus 1.2835 cm) (Fig. 4). Furthermore, the time between preoperative and follow-up measurements showed no significant correlation with change in diameter ($p > 0.05$, $f = 0.149$) (Fig. 5).

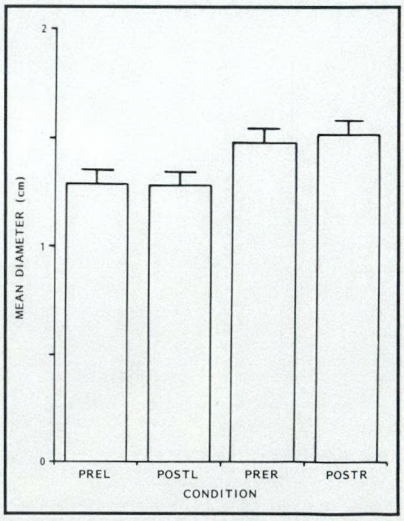

FIG. 4. Mean common iliac artery diameters for 23 right and 23 left arteries measured pre- and postoperatively show no significant change. PREL = preoperative, left, POSTL = postoperative, left, PRER = preoperative, right, POSTR = postoperative, right.

Discussion

Aneurysms of the common iliac arteries are, more often than not, associated with abdominal aortic aneurysm.[3-6] Isolated common iliac artery aneurysms have an etiologic association with atherosclerosis and share with other atherosclerotic aneurysms a tendency to rupture.[3,5,7-9] There is no evidence, however, that aneurysmal change develops in normal common iliac arteries, even though occlusive disease may occasionally develop.

Since 1978 surgeons at The Wellesley Hospital have used tube repair for aortic aneurysms, unless there is occlusion, serious stenosis or aneurysmal change in one or both common iliac arteries.

There are several advantages to the use of a tube prosthesis. The operation is simpler and hence quicker and is attended by less blood loss and a lower risk of damage to the hypogastric plexus.

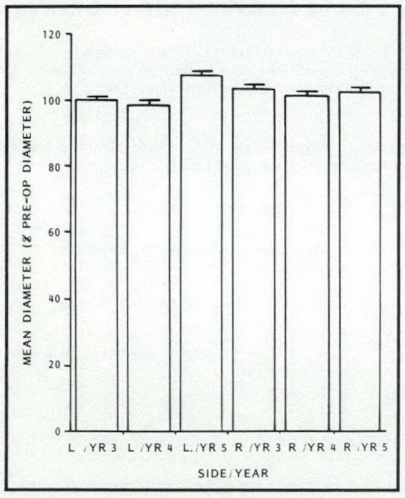

FIG. 5. Mean common iliac artery diameters show no significant increase on either side, regardless of whether follow-up was at 3, 4 or 5 years.

It can very easily be performed extraperitoneally. The disadvantages of the procedure lie in the risks of not treating serious atherosclerosis or of leaving dilatation in these arteries. Subsequent aneurysmal change would require a further operation. In our experience further surgery has never been necessary, nor have there been complications because of atherosclerotic occlusive disease in these arteries.

Our study has addressed the concern that aneurysmal change of the common iliac arteries might occur after repair of an abdominal aortic aneurysm with a tube prosthesis. We found no tendency for the common iliac arteries to dilate during 3 to 5 years after tube repair of the abdominal aorta, even if the common iliac arteries had been somewhat dilated preoperatively.

Occasionally, we actually recorded a small decrease in size of the iliac arteries at follow-up examination. Obviously, some reduction in intraluminal diameter might occur as a result of progression of atherosclerotic occlusive disease, but in no case was such disease clinically important.

It can be argued that those patients who had significant atherosclerotic occlusive disease and those in whom aneurysmal change is likely had already been excluded from our series, by virtue of having had an aortobifemoral bypass. This does not, however, affect the conclusion that tube repair of the abdominal aortic aneurysm is appropriate in selected patients.

The lack of a marked increase in diameter suggests that whatever the factors are that lead to iliac dilatation in the presence of an abdominal aortic aneurysm they may not be as important once the aneurysm has been repaired.

This study therefore supports the use of the more conservative tube repair for aortic aneurysms by suggesting that it is not followed by marked aneurysmal change in the common iliac arteries for up to 5 years postoperatively.

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℞Cefizox™

sterile ceftizoxime sodium

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION

In vitro studies indicate that the bactericidal action of ceftizoxime results from inhibition of cell-wall synthesis in aerobic and anaerobic gram-positive and gram-negative organisms. *In vitro*, ceftizoxime shows a strong affinity for penicillin-binding proteins Ia, Ibs and 3 of *E. coli*.

INDICATIONS AND CLINICAL USES

Cefizox™ (sterile ceftizoxime sodium) may be indicated in the treatment of the infections listed below when caused by susceptible strains of the designated microorganisms:

LOWER RESPIRATORY TRACT INFECTIONS caused by *Streptococcus* sp. (including *S. pneumoniae* but excluding enterococci); *Klebsiella* sp.; *Proteus mirabilis; Escherichia coli; Haemophilus influenzae* (including ampicillin-resistant strains); *Staphylococcus aureus* (including penicillinase-producing but excluding methicillin-resistant strains); *Serratia* sp.; and *Enterobacter* sp.

URINARY TRACT INFECTIONS caused by *Escherichia coli; Staphylococcus epidermidis; Pseudomonas aeruginosa; Proteus mirabilis; Klebsiella* sp.; *Serratia marcescens;* and *Enterobacter* sp.

Due to the nature of the underlying conditions which usually predispose patients to *Pseudomonas* infections of the urinary tract, a good clinical response accompanied by bacterial eradication may not be achieved despite evidence of *in vitro* sensitivity.

INTRA-ABDOMINAL INFECTIONS caused by *Escherichia coli; Staphylococcus epidermidis; Streptococcus* sp. (excluding enterococci); *Klebsiella* sp.; *Bacteroides* sp. (including *B. fragilis*); Peptococcus sp.; and *Peptostreptococcus* sp.

SEPTICEMIA caused by *Streptococcus* sp. (excluding enterococci but including *S. pneumoniae*); *Staphylococcus aureus* (excluding methicillin-resistant strains); *Escherichia coli; Bacteroides* sp. (including *B. fragilis); Klebsiella* sp.; and *Serratia marcescens.*

SKIN STRUCTURE INFECTIONS caused by *Staphylococcus aureus* (excluding methicillin-resistant strains); *Staphylococcus epidermidis; Escherichia coli; Klebsiella* sp., (including *K. pneumoniae); Streptococcus* sp. (excluding enterococci but including Group A ß-hemolytic *Streptococcus pyogenes); Proteus mirabilis; Serratia* sp.; *Enterobacter* sp.; *Bacteroides* sp. (including *B. fragilis); Peptococcus* sp., and *Peptostreptococcus* sp.

BONE AND JOINT INFECTIONS caused by *Staphylococcus aureus* (excluding methicillin-resistant strains); *Proteus mirabilis; Peptococcus* sp.; and *Peptostreptococcus* sp.

Specimens for bacteriologic culture should be obtained prior to therapy in order to identify the causative organisms and to determine their susceptibilities to ceftizoxime. Therapy with Cefizox™ may be initiated before results of the susceptibility studies are known. However, modification of the treatment may be required once these results become available.

CONTRAINDICATIONS

Cefizox™ (sterile ceftizoxime sodium), is contraindicated in persons who have shown hypersensitivity to ceftizoxime or other members of the cephalosporin group of antibiotics.

WARNINGS

Before therapy with Cefizox™ (sterile ceftizoxime sodium) is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins, or other drugs. Cefizox™ should be given cautiously to penicillin-sensitive patients. Antibiotics, including Cefizox™, should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to Cefizox™ occurs, its administration should be discontinued. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of Cefizox™ (and other antibiotics). Therefore, it is important to consider this diagnosis in patients administered Cefizox™ who develop diarrhea.

Treatment with broad-spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance or when it is severe, consideration may be given to the administration of oral vancomycin or other suitable therapy. Other possible causes of colitis should also be considered.

PRECAUTIONS

General: Transient elevations of BUN and serum creatinine have been observed in clinical studies. However, there is no other evidence that Cefizox™ (sterile ceftizoxime sodium) has produced alterations in renal function. Renal status should be periodically evaluated, especially in seriously ill patients.

Prolonged use of Cefizox™ may result in the overgrowth of nonsusceptible organisms including species originally sensitive to the drug. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Cefizox™ should be administered with caution to individuals with a history of gastrointestinal disease, particularly colitis.

Impaired Renal Function: Since ceftizoxime is excreted primarily in the urine, patients with impaired renal function (i.e., creatinine clearance ≦1.32 mL/s or ≦ 79 mL/min) should be placed on a special dosage schedule recommended under DOSAGE AND ADMINISTRATION. Normal dosages in these individuals are likely to produce excessive serum concentrations of ceftizoxime.

Drug Interactions: The concomitant administration of some cephalosporins and aminoglycosides has caused nephrotoxicity. The effect of administering Cefizox™ concomitantly with aminoglycosides is not known.

Pregnancy: The safety of Cefizox™ in pregnancy has not been established. The use of Cefizox™ in pregnant women requires that the likely benefit from the drug be weighed against the possible risk to the mother and fetus. The pharmacokinetics of Cefizox™ in pregnant patients has not been investigated. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus caused by ceftizoxime. Animal reproduction studies, however, are not always predictive of human response.

Labour and Delivery: The safety and efficacy of Cefizox™ use during labour and delivery has not been investigated.

Nursing Mothers: Ceftizoxime is excreted in human milk in low concentrations (less than 4% of serum concentrations at 1 hour after dosing). The clinical significance of this is unknown; therefore caution should be exercised if Cefizox™ is to be administered to a nursing woman.

Infants and Children: The safety of Cefizox™ in infants less than 6 months of age has not been established. In children six months of age and older, treatment with Cefizox™ has been associated with transient elevated levels of eosinophils, SGOT, SGPT and CPK (creatine phosphokinase). The CPK elevation may be related to intramuscular administration.

Elderly Patients: The elimination of ceftizoxime may be reduced due to an age-dependent reduction in renal function.

ADVERSE REACTIONS

Cefizox™ (sterile ceftizoxime sodium) is generally well tolerated.

Adverse Reaction	Incidence ≦1%	Incidence >1% but <5%
Hypersensitivity:		Rash Pruritus Fever
Liver:		Transient elevation of SGOT, SGPT and alkaline phosphatase
Blood:	Neutropenia Leukopenia Thrombocytopenia	Transient eosinophilia Thrombocytosis Positive direct Coombs' test
Renal:	Transient elevation of BUN and creatinine	
Local:		Injection site: burning, cellulitis, phlebitis (with IV administration), pain, induration, tenderness, parasthesia
Genitourinary:	Vaginitis	
Gastrointestinal:	Diarrhea, Nausea, Vomiting, Pseudomembranous colitis	

No disulfiram-like reactions have been reported with Cefizox™

TREATMENT OF OVERDOSAGE

No case of acute overdosage has been reported to date; consequently there is no specific information available on symptoms or treatment. In cases of suspected overdosage, supportive therapy should be instituted according to symptoms. Serum ceftizoxime levels can be reduced by hemodialysis.

DOSAGE AND ADMINISTRATION

Cefizox™ (sterile ceftizoxime sodium) may be administered either intramuscularly or intravenously after reconstitution.

Dosage and route of administration should be determined by the condition of the patient, severity of the infection and susceptibility of the causative organism(s). The intravenous route may be preferable for patients with bacterial septicemia, or other severe or life threatening infections.

The usual course of treatment should be 7-14 days, and should normally continue at least 48 hours after evidence of bacterial eradication has been obtained. For ß-hemolytic streptococcal infections, a minimum of 10 days of treatment is recommended.

DOSAGE

Adults: The recommended daily dosage of Cefizox™ is 1 to 12 grams administered in equally divided doses every 8 or 12 hours (see Table 1 below).

TABLE 1

Type of Infection	Daily Dose (Grams)	Frequency and Route
Uncomplicated Urinary Tract	1	500 mg q12h, IV or IM
Other Sites	2-3	1 g q8h or q12h, IV or IM
Severe or Refractory	3-6	1 g q8h, IV or IM, to 2 g q8h or q12h, IV or IM*
Life-Threatening	9-12	3 or 4 g q8h IV

*When administering 2 g intramuscularly, the dose should be divided and injected into different large muscle masses.

Because of the serious nature of urinary tract infections due to *Pseudomonas aeruginosa* and because many strains are only moderately susceptible to Cefizox™, higher dosage may be appropriate when urinary tract infections are caused by these organisms. Other therapy should be instituted if the response is not prompt.

Adults with Impaired Renal Function: In patients in whom the creatinine clearance is 1.32 mL/s (79 mL/min) or less, the dosage of Cefizox™ must be reduced. Following an initial loading dose of 500 mg to 1.0 g IM or IV, the maintenance dosing schedule presented in Table 2 should be followed in patients with reduced renal function.

TABLE 2

Renal Function	Creatinine Clearance mL/s	Creatinine Clearance mL/min	Less Severe Infections	Life-Threatening Infections
Mild Impairment	0.83-1.32	50-79	500 mg q8h	750 mg to 1.5 g q8h
Moderate to severe impairment	0.08-0.82	5-49	250 or 500 mg q12h	500 mg to 1.0 g q12h
Hemodialysis patients*	0-0.07	0-4	500 mg q48h or 250 mg q24h	500 mg to 1.0g q48h or 500 mg q24h

*In patients undergoing hemodialysis no additional supplemental dosing is required. DOSING, HOWEVER, SHOULD BE SCHEDULED SO THAT THE PATIENT RECEIVES THE DOSE AT THE END OF THE DIALYSIS. When started 24 hours after administration of 1 g of Cefizox™, hemodialysis has been shown to reduce serum levels by 50%.

When only the serum creatinine level is available, creatinine clearance may be calculated from the following formulae (for patients 18 years and over only). The serum creatinine level should represent renal function at the steady state.

Males:

$$\text{Creatinine Clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Creatinine Clearance (mL/s)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{49 \times \text{serum creatinine } (\mu\text{mol/L})}$$

Females: 0.85 of the above values

Infants and Children: The following dosage schedule is recommended:

TABLE 3

Age Group	Unit Dosage	Frequency and Route
Infants (6 mo-2 yrs.), and Children (2-12 yrs.)	50 mg/kg IV or IM	q6h or q8h, IV or IM

The pediatric dosage should not exceed the maximum adult dosage for serious infections.

ADMINISTRATION

Intramuscular: The reconstituted solution of Cefizox™ should be injected well within the body of a relatively large muscle, such as the gluteus. When administering 2 g IM doses, the dose should be divided equally and then injected into different large muscle masses.

Intravenous: Injection (bolus): The reconstituted solution of Cefizox™ should be injected slowly over 3 to 5 minutes, directly or through the tubing system by which the patient is receiving another compatible intravenous solution. During administration of the solution containing Cefizox™, it is desirable to temporarily discontinue administration of the other solution.

Intermittent or continuous infusion: The further diluted reconstituted solution of Cefizox™ should be administered over a 20 to 30 minute period.

NOTE: Cefizox™ solutions should not be physically mixed with any other drug. There is a known incompatibility with aminoglycoside antibiotics. Therefore, they should not be physically mixed with Cefizox™ solutions nor administered at the same site.

PHARMACEUTICAL INFORMATION

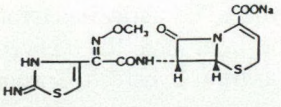
CHEMISTRY

Trade Name: CEFIZOX™

Proper Name: Ceftizoxime Sodium

Chemical Name: Sodium [6R-(6α, 7β(Z))]-7-[[(2,3-dihydro-2-imino-4-thiazolyl) (methoxyimino) acetyl]amino]-8-oxo-5-thia-1-azabilcyclo[4.2.0] oct-2-ene-2-carboxylate

Structural Formula:



Molecular Formula: $C_{13}H_{12}N_5O_5S_2Na$

Molecular Weight: 405.38

Description: Ceftizoxime Sodium is a white to pale yellow crystalline powder.

Composition: Cefizox™ vials contain ceftizoxime sodium (expressed in terms of free acid). The sodium content of each gram of Cefizox™ is approximately 60 mg (2.6 mEq sodium ion).

Solutions of Cefizox™ range from colourless to pale yellow, depending upon the diluent and volume used. The solution should be discarded if it becomes cloudy. The pH of freshly reconstituted solutions usually ranges from 6.0 to 8.0.

A solution of 1 g Cefizox™ in 13 mL Sterile Water for Injection is isotonic.

RECONSTITUTION

STANDARD VIALS (1 GRAM and 2 GRAMS)

For Intramuscular Injection: Reconstitute with Sterile Water for Injection or Bacteriostatic Water for Injection.

Reconstitution Table for Standard Vials - I.M. Injection

Vial Size	Diluent to be Added to Vial	Approximate Available Volume	Approximate Average Concentration
1 g	3.0 mL	3.7 mL	270 mg/mL
2 g	6.0 mL	7.4 mL	270 mg/mL

Shake well until dissolved.

For Intravenous Injection: Reconstitute only with Sterile Water for Injection.

Reconstitution Table for Standard Vials - I.V. Injection

Vial Size	Diluent to be Added to Vial	Approximate Available Volume	Approximate Average Concentration
1 g	10 mL	10.7 mL	95 mg/mL
2 g	20 mL	21.4 mL	95 mg/mL

Shake well until dissolved.

For Intravenous Infusion: Reconstitute as for intravenous injection. Further dilute the reconstituted solution to 50 to 100 mL with one of the "Solutions for Intravenous Infusion" (see below).

TABLE 4: Solutions for Intravenous Infusion

Sodium Chloride Injection
5% or 10% Dextrose Injection
5% Dextrose and 0.9%, 0.45% or 0.2% Sodium Chloride Injection
Ringer's Injection
Lactated Ringer's Injection
10% Invert Sugar in Sterile Water for Injection
5% Sodium Bicarbonate in Sterile Water for Injection
5% Dextrose in Lactated Ringer's Injection ONLY when reconstituted with 4% Sodium Bicarbonate Injection.

STABILITY OF SOLUTIONS

Storage: All reconstituted solutions and those further diluted should be used within 24 hours if stored at room temperature or within 48 hours if refrigerated. These storage limits are from the time of the initial reconstitution.

Incompatibility: Cefizox™ should not be added to blood products, protein hydrolysates or amino acids. Cefizox™ should not be mixed together with an aminoglycoside.

DOSAGE FORMS

Availability: Cefizox™ is available as a sterile powder in Standard Vials of 1 gram or 2 grams, containing ceftizoxime as sodium salt.

Storage: Cefizox™ powder for injection should be stored at room temperature (15°-30°C).

References:

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Hot-Tip Laser Angioplasty for Peripheral Vascular Disease: Clinical Experience With 18 Patients

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Between May 1988 and March 1989, the authors treated 18 patients who suffered from disabling claudication or rest pain. They used the laser hot-tip angioplasty technique, in which a metal tip on the laser transforms laser energy into heat. Nineteen lower extremities were so treated. Six patients had suffered iliac occlusion, 11 had disease in the superficial femoral artery and 1 in the popliteal artery.

Laser angioplasty was successful in 7 of 13 lower limbs with infrailiac lesions and in 4 of the 6 limbs with iliac artery occlusion; the other 2 underwent bypass grafting (aortoiliac in 1 and aortobifemoral in the other). No loss or limb or death occurred, but immediate complications of perforation or dissection were frequent.

De mai 1988 à mars 1989, les auteurs ont traité 18 patients souffrant de claudication intermittente ou douleur de repos. Ils ont employé la technique connue sous le nom de "angioplastie thermique au laser" qui consiste à employer en embout métallique placé à l'extremité d'une fibre optique et qui transforme l'énergie laser en chaleur. Dix-neuf membres inférieurs ont été traités. Six patients présentaient une occlusion iliaque, 11 une maladie de l'artère fémorale superficielle et 1 une lésion de l'artère poplité.

L'angioplastie au laser a été effectuée avec succés chez 7 des 13 lésions infrailiaques et chez 4 des 6 occlusions iliaques, les deux autre patients ayant du subir un pontage (aortoiliaque pourun et aortobifémoral pour l'autre). Aucune perte de membre ni mortalité n'est survenue, mais les complications immédiates de perforation ou dissection furent fréquentes.

In 1980, Macruz and colleagues[1] reported on the use of laser energy to ablate atherosclerotic plaques. Interest in laser angioplasty was further stimulated by Choy and associates[2,3] who reported their in-vitro studies on coronary arteries of cadavers and in-vivo studies on animals using flexible fiberoptics. Ginsburg and associates[4] were the first to report a successful clinical laser angioplasty procedure, performed on a severely stenosed deep femoral artery. In February 1987, the American Food and Drug Administration (FDA) gave its approval to the use of laser thermal recanalization of occluded arteries.[5] In this technique an optic fibre with a metal tip transforms laser energy into heat. In this paper, we describe our experience with this technique in 18 patients with atherosclerotic peripheral vascular disease.

Patients and Methods

Patient Selection

The study group included 15 men, ranging in age from 46 to 77 years (mean 59 years), and 3 women ranging in age from 45 to 85 years (mean 64 years) (Table I). Criteria for selection included any or all of the following: (a) disabling claudication of thigh or calf or pain at rest; (b) minor tissue loss (e.g., nonhealing ulcer or focal gangrene with diffuse pedal ischemia).

Patients were classified according to the clinical categories of chronic limb ischemia described by Rutherford[6] (Table I).

Equipment

A continuous wave neodymium: yttrium-aluminum-garnet (Nd:YAG) laser (Heraus, LaserSonics Inc., Santa Clara, Calif.) was used in all cases, and all procedures were done using a mobile x-ray unit (BV-25, Phillips Medical Systems, Shelton, Conn.).

Two types of delivery system were used: Laserprobe-SLR 2.5 (Trimedyne, Santa Ana, Calif.) and Laserprobe-PLR 2.5 Flex (Trimedyne). The optical adaptor between the laser and the delivery system was from Dynetech, Toronto, Ont.

Laser Angioplasty

In 12 patients, the lower extremity was entered through the femoral artery. Surgical dissection of the artery was favoured over the percutaneous technique in obese patients or when iliac occlusion prevented palpation of a femoral pulse. After systemic heparinization (100 units/kg), the femoral artery was punctured with a Seldinger needle. A no. 8 French introducer (Cordis

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Corp., Miami, Fla.) was then inserted in either a cephalad or a caudad direction according to which arterial segment was occluded. It was connected to a constant pressure perfusion system. A baseline angiogram was then obtained.

The PLR-2.5 Flex laser probe was used for stenoses or when the guide wire (Terumo 0.035; Terumo Corp., Tokyo, Japan) could cross the occluded segment. A no. 5 French straight catheter (Cook Inc., Bloomington, Ind.) was then inserted over the guide wire which was replaced by a soft-tipped Bentson guide wire measuring 0.089 cm (0.035 inch) in diameter (Cook Inc.). The SLR-2.5 probe was used when the guide wire could not cross an occlusion.

Laser output was set at 13 W. Upon activation of the laser, the probe was sequentially placed in contact with the lesion and moved away from it, using a back and forth action, in order to avoid burning the arterial wall.

Balloon Angioplasty

After recanalization of the artery, balloon angioplasty was performed at the lased site. Conventional techniques were employed, using the femoral artery sheath already in place. The size of the balloon catheter (Bard, USCI Division, Billerica, Mass.) was determined by the diameter of the vessel measured on arteriography proximal to the occlusion. When a surgical approach was used, bleeding was controlled by a single suture of 5-0 Prolene placed after introducer withdrawal.

Patients were maintained on heparin for 24 hours postoperatively. One capsule of Entrophen-10 (Frosst) was then given daily.

Vessel Patency

Vessel patency was determined preoperatively by measurement of the ankle/arm pressure index. Determinations were repeated at postprocedure follow-up, which ranged from 6 to 15 months. This indicated whether achieved improvement had been maintained in the appropriate limb segment. The criteria for continued patency were a normalized segmental limb pressure index or one at least 0.1 above the preoperative index and no more than 0.1 less than the maximum postoperative index; the former without the latter was considered as "deterioration" rather than "failure".

Results

Patient Experience

One of the 18 patients underwent hot-tip laser angioplasty on the contralateral limb 5 months after the first intervention. The actual laser procedure usually took no more than 3 to 5 minutes, although total operative time was, on average, 116 minutes. Local anesthesia was used in two patients who complained of moderate pain at the operative site.

Table I. Patient Data

Case	Age, yr	Sex	Clinical categories: Grade	Clinical categories: Group	Artery	Stenosis: %	Stenosis: Length, cm	Residual stenosis, %	Approach	Type of probe	Complications: Type	Complications: Treatment
1	61	M	II	4	RSF,RP	100	3.4	90	S	SLR	–	–
2	64	M	II	4	RSF	100	5	80	P	PLR	–	–
3	65	M	I	3	LSF	100	4	NP	P	SLR	Perforation	Observation
4	54	M	I	1	LI	100	8	<10	P	PLR	–	–
5	76	M	I	3	RSF	100	3	<10	P	PLR	MI	Medical
6	77	M	I	2	LSF	100	4	30	P	SLR	–	–
7	63	F	I	2	RP	98	2	5	S	PLR	Hematoma	Evacuation
8	85	F	I	3	RSF	100	2	0	P	SLR	–	–
9	45	F	I	3	LI	100	9	<10	S	PLR	–	–
10	53	M	I	1	LSF	100	5	NP	S	SLR	Perforation	FPB
11	64	M	II	4	LSF	100	4	<10	S	SLR	Hematoma dissection	Observation
12	46	M	I	1	RI	100	6	NP	P	SLR	Perforation	AIB
13	48	M	I	3	RSF	100	9	NP	S	NP	Occlusion not visualized	FPB
14	53	M	I	3	LI	100	8	NP	S	SLR	Perforation	ABF
15	53	M	I	3	RI	100	8	<10	S	PLR	–	–
16	60	M	I	3	LSF	99	9	<10	S	PLR	–	–
17	51	M	I	2	LSF	100	6	NP	P- S	SLR	Hematoma dissection	Endarterectomy
18	77	M	II	4	RSF	100	20	NP	S	SLR	Perforation	FPB
19	57	M	I	3	RI	99	2	<10	S	PLR	Embolism	Observation

RI = right iliac artery, LI = left iliac artery, RSF = right superficial femoral artery, LSF = left superficial femoral artery, RP = right peroneal artery, NP = not performed, S = surgical, P = percutaneous, MI = myocardial infarction, FPB = femoropopliteal bypass, AIB = aortoiliac bypass, ABF = aortobifemoral bypass.

However, pain ceased when the laser was turned off, and the procedure was not interrupted.

Laser Angioplasty

Sixteen of the 19 limbs treated had complete arterial occlusion and 3 had severe stenosis (98% to 99%) (Table I). Eleven (58%) limbs were successfully treated (Figs. 1 and 2).

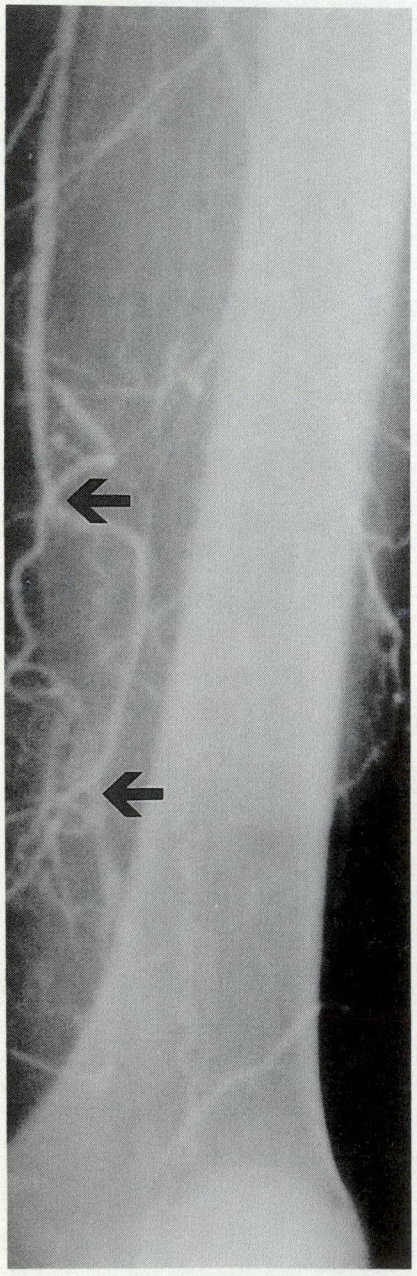

FIG. 1. Occlusion (arrows) of 6-cm segment of right superficial femoral artery.

Complications during the laser procedure included the following: perforation of the vessel wall by the Laserprobe, documented by angiography (five instances) (Fig. 3); local hematomas (three); dissection of the arterial wall with no distal recanalization, demonstrated at angiography (two) (Fig. 4); greater than 50% residual stenosis at the site of angioplasty (two); inability to find the actual point of occlusion because of the proximity of a collateral vessel (one); myocardial infarction (one); distal embolism (one).

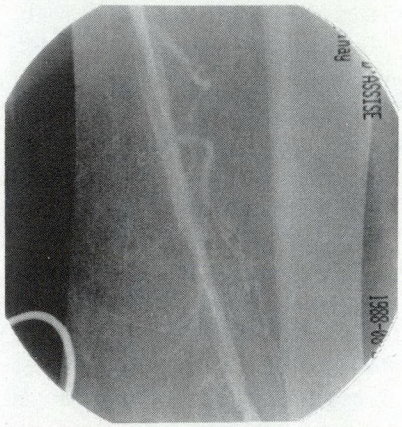

FIG. 2. Successful recanalization immediately after laser assisted balloon angioplasty.

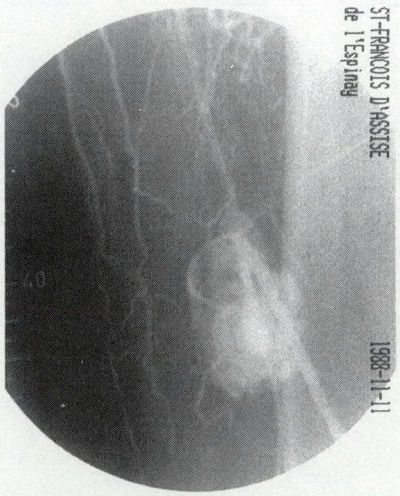

FIG. 3. Perforation of right superficial femoral artery by laser probe. Note localization of contrast material by surrounding tissues at site of perforation.

Except for one dissection related to the percutaneous technique, the perforations and the other dissection occurred when the Laserprobe-SLR (without a guide wire) was used (Table I).

The patients received treatment appropriate to the complications they suffered (Table I). The two who had iliac perforation underwent a bypass procedure (aortobifemoral and aortoiliac respectively). In one the iliac perforation resulted in a localized hematoma; in the other a larger retroperitoneal hematoma developed. The site of iliac perforation was sutured before each bypass.

Among the three patients who had perforation of the superficial femoral artery, two had a femoropopliteal bypass and the other was followed up by observation. Superficial femoral artery perforation was treated expectantly in each case.

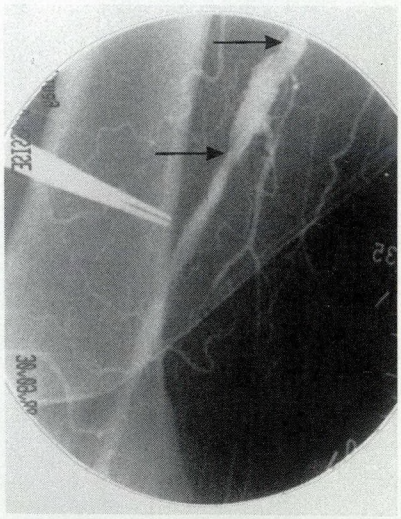

FIG. 4. Subintimal dissection (between arrows) leading to failure of laser-assisted balloon angioplasty. Laser probe entered plane of least resistance at site of occlusion (upper arrow). Subintimal plane is route often chosen by laser probe or guide wire to cross occlusion. In this case, despite apparent good result, thrombosis occurred peroperatively. It was impossible to cross dissected segment with either laser probe guide wire.

For the patient in whom the exact origin of the occlusion could not be localized, femoropopliteal bypass was performed. The patient who suffered dissection of the distal iliac and common femoral arteries underwent iliofemoral endarterectomy with a venous patch. The patient who had dissection at the site of angioplasty was treated expectantly (Fig. 4).

The results for the balloon dilatations are reported in Table I. The two patients who had residual stenoses of 90% and 80% were diabetic. They underwent femorotibial bypass for pain at rest 6 and 12 months after angioplasty. All other patients had residual stenoses of 10% or less with the exception of one who had 30% residual stenosis.

Distal embolism was diagnosed in the recovery room in one patient and the clinical findings were confirmed by Doppler examination. Symptoms and signs disappeared 1 hour later, probably owing to fragmentation of the embolus. The embolism could have been caused either by the balloon dilatation or by the laser procedure itself.

Two hematomas developed after surgical dissection of the artery and one after the percutaneous approach. One was sufficiently severe to require reoperation and hemostasis; the other two were treated expectantly.

Pre- and postoperative determinations of ankle/arm pressure indices were used as determinants of improved blood flow and continued vessel patency of the treated extremity. A persistent elevation of the ankle/arm index above 0.1 from the preoperative value, signifying improvement, was noted in the four patients who had successful iliac recanalization and who noted a marked improvement in their clinical status (Fig. 5). However, only two of the seven patients followed up after femoropopliteal laser angioplasty had a rise of 0.1 or more in their ankle/arm index (Fig. 6). The length of occlusion of the recanalized femoropopliteal segments varied from 2 to 9 cm. Three of our patients were classified as grade I, category 1, before angioplasty. Their preoperative ankle/arm indices were 0.77, 0.64 and 0.63. We believed that these younger, active patients, who were incapacitated by claudication, might benefit from laser angioplasty. However, only one had a successful outcome. The two other patients suffered perforation and therefore underwent bypass grafting.

Discussion

Although balloon angioplasty alone has proven an effective means of treating most patients with localized stenotic or occlusive lesions, the possibility of ablating atherosclerotic plaque rather than merely expanding the arterial lumen has intrigued investigators.[7]

The laser studies of Sanborn, Cumberland and Greenfield,[8-11] aroused considerable interest in laser thermal angioplasty. Specific advantages have been reported when the laser is used as an adjunct to angioplasty,[11,12] including the ability of the laser to traverse difficult lesions, such as long-segment occlusions, thus extending the use of angioplasty. Ablation and "debulking" of atheromatous plaque by laser has been proposed as a method to enhance both immediate and long-term results of balloon angioplasty.[13] Ablation of plaque and a reduction in platelet adhesions at the angioplasty site[14] may reduce the release of potent smooth-muscle-cell mitogens which stimulate restenosis. Thermally induced changes of smooth muscle cells and collagen in vessel walls may alter vessel compliance and reduce arterial responsiveness to released vasoconstrictors, thus increasing luminal diameter.[15] Although these factors may contribute to the efficacy of laser angioplasty, the actual biologic mechanisms remain to be assessed.[7]

To date, no randomized prospective trials have addressed the question of whether the adjunctive use of lasers in balloon angioplasty offers any advantage over standard guide-wire techniques.[7] Clinical efficacy, therefore, must be assessed on comparisons between various

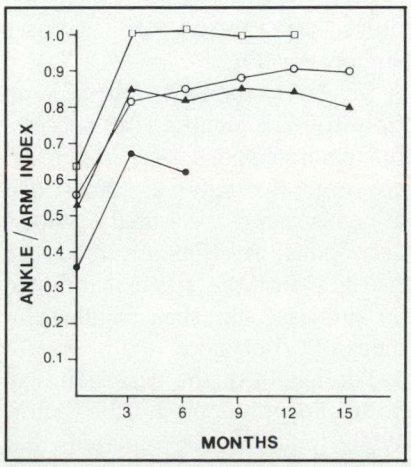

FIG. 5. Follow-up serial ankle/arm index determinations of four patients who had successful femoropopliteal laser-assisted balloon angioplasty.

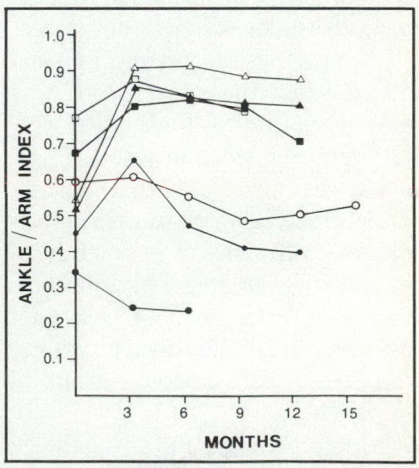

FIG. 6. Follow-up serial ankle/arm index determinations of seven patients who had successful iliac laser-assisted balloon angioplasty.

studies that have used one method or the other.[7]

Cragg and associates[7] compared balloon angioplasty for femoropopliteal occlusions to laser-assisted angioplasty of similar lesions. The immediate angiographic and clinical success rates appeared to be similar (72%). Comparison of long-term patency after angioplasty of vessel occlusions also showed similar outcomes. Recently, Morgenstern and associates[16] reported an immediate technical success rate of 91% for recanalization of femoropopliteal occlusions 1 to 10 cm long, using the conventional guide-wire technique.

Timbadia and colleagues[17] recently reported their 2-year experience with 1380 laser-assisted peripheral angioplasties performed on 671 patients. Their recanalization rate was 76% which is comparable to that of other series. The immediate patency rate in our series was 58%. Factors that may account for the difference are the learning curve for adequate performance of the technique and the type of laser probe used to cross the occlusion. Timbadia and colleagues attempted to cross the occlusion with a guide wire before proceeding to laser angioplasty. The number of patients treated using the guide wire was not stated.

In our series, all perforations occurred when the Laser probe was used without the guide wire. Our perforation/dissection rate (37%, 7 of 19) was higher than that generally reported (12%). However, Perbellini and colleagues,[18] in a study of 85 patients, reported a perforation/dissection rate of 25.4%. Seeger and associates[19] described a perforation rate of 22% among a group of 46 patients.

White, White and Kopchok[20] noted that the unguided laser probe tends to follow the path of least resistance. Tobis and associates[21] attempted to recanalize arterial segments of excised human peripheral arteries using a 1.5 mm laser probe heated by an argon laser, producing 10 to 12 W. The arterial segments were 5 to 10 cm long and complete occlusion was documented by angiography. Transmural perforation occurred in 8 of 11 (73%) arterial segments treated with a laser-heated probe. Arterial perforation occurred in one of five (20%) artery segments approached without heating, using a standard 0.089 cm (0.035 inch) guide wire and catheter technique. In 10 of 11 (91%) heated and all 5 non-heated artery segments, the wire and probe appeared mechanically to deflect away from hard fibrocalcific plaque and to dissect between the intima and media. According to Tobis and colleagues,[21] mechanical dissection may be an important factor during laser thermal artery recanalization.

Timbadia and colleagues[17] reported a 67% patency rate after iliac artery recanalization for occlusive disease and 77% after recanalization of an occluded superficial femoral artery at follow-up ranging from 6 to 24 months. In our series, at follow-up ranging from 6 to 15 months, the four patients who had their iliac artery successfully recanalized were clinically much improved as a result of iliac laser angioplasty (Fig. 5).

Of seven patients followed up from 6 to 15 months after successful femoropopliteal laser angioplasty (Fig. 6), only 2 (29%) had a consistently elevated ankle/arm index. At 3-month follow-up five (71%) of the seven manifested an increase in their ankle/arm index of 0.1 or more.

The length of the occlusion may be an important prognostic factor. White and White[4] reported that treatment of occlusive lesions 1 to 3 cm long resulted in a 1-year patency rate of 90% to 95% in contrast to a 46% patency after treatment of occlusions longer than 7 cm. In our series, two patients who maintained their ankle/arm index had occlusions 2 and 3 cm long. Three patients had occlusions of 4 cm, one of 9 cm and one patient had a stenosis of the popliteal artery 2 cm long.

More frequent recurrences at the femoropopliteal level than at the iliac region are explained in part by the size of the vessel.[5] Disappointing patency rates of 20% to 30% have been reported for laser angioplasty at the level of the tibial vessels.[5] Furthermore, Datena and associates[22] noted that the pattern of restenosis corresponded to the length of vessel exposed to the thermal probe rather than to the original lesion. They concluded that because of the high rate of recurrent stenosis and the pattern of apparent thermal injury, extreme caution is warranted if use of the thermal probe is to be continued.

To document the follow-up of these patients and the pattern of recurrence better, Fehrenbacher indicated that the FDA has recently recommended follow-up angiography 6 months after laser angioplasty in at least 50% of the patients subjected to the procedure.[22]

Rienk and colleagues[23] suggested that laser recanalization of a noncalcified obstruction is more effective with a sapphire contact probe than with a metal tip probe because the former produces higher flow and larger channels. Lammer and Pilger[24] compared sapphire tip and metal laser probes and concluded that the saphire probe enabled ablation of a larger volume of tissue surrounded by only a small zone of thermal necrosis. Coupled to a continuous wave Nd:YAG laser, the delivery system consists of an optic fibre at the end of which is placed an specially devised sapphire.[25-29] In an Austrian multicentre trial[30] 286 patients with femoropopliteal occlu-

sions were studied. Immediate recanalization rates (84%), and patency rates at 2 years (74%) were comparable to hot (metal) tip laser angioplasty.

In contrast to continuous wave lasers, pulsed lasers achieve tissue vaporization with less thermal damage to the surrounding arterial wall.[31-34] Also, thrombogenicity appears to be reduced at the irradiated site.[35] The excimer laser (308 nm) would allow vasodilatation of an irradiated arterial segment, and continuous wave lasers, through a thermal effect, may cause arterial spasm.[36] The excimer laser produces a photoablative rather than a photothermal effect and can penetrate calcified atheroma.[37-43] Other pulsed lasers currently under investigation include dye (480 nm), argon (514 nm), Nd:YAG (355, 532, 1064 nm) and Er:YAG (2940 nm) lasers.[37]

Conclusions

Our results confirm the feasibility of hot-tip laser-assisted balloon angioplasty for obstructed arteries of the iliac and femoropopliteal segments. Although complications did not endanger the life or limbs of our patients, their frequency, particularly when no guide wire was used, raises concern. Prospective randomized trials are needed. Lasers should remain investigational devices until their clinical usefulness has been established.

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Spontaneous Rupture of Splenic Artery Aneurysm: Maternal and Fetal Survival

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Because the diagnosis of ruptured splenic artery aneurysm in pregnancy is seldom made before operation, maternal and fetal mortality continues to be high. The authors describe the case of a 22-year-old woman who had a ruptured splenic artery aneurysm at 32 weeks' gestation. The attending obstretician considered this condition in the differential diagnosis and it was confirmed by ultrasonography, leading to a successful outcome.

Comme le diagnostic des ruptures d'anévrismes de l'artère splénique durant la grossesse est rarement posé avant la chirurgie, la mortalité maternelle et foetale continue d'être élevée. Les auteurs décrivent le cas d'une femme de 22 ans qui a subi une rupture de l'artère splénique au cours de la 32e semaine de gestation. Cette possibilité ayant été envisagée par l'obstétricien dans son diagnostic différentiel, puis confirmée l'échographie, l'issue fut heureuse.

Rupture of splenic artery aneurysm in pregnancy, although an uncommon condition, is associated with a very high maternal mortality and only occasional fetal survival. The most recent published report of maternal and fetal survival was in 1986.[1] Very rarely is the diagnosis of ruptured splenic artery aneurysm made before operation. This case report documents the preoperative diagnosis and the prompt surgical intervention that resulted in the eighth reported successful maternal and fetal outcome.

Case Report

A 22-year-old primagravida was seen in the emergency room at 32 weeks' gestation with a 24-hour history of continuous, dull, low back pain. On admission, vital signs were stable and the fetal heart rate was 132 beats/min. The non-stress test was reactive. Abdominal examination revealed epigastric tenderness and a soft, nontender uterus. The cervix was closed, uneffaced, with the presenting part at −3 station. Initial routine blood and urine tests gave normal results. Shortly after the patient received a dose of Demerol intramuscularly, her blood pressure fell to 80/50 mm Hg. A repeat complete blood count (90 minutes after admission) revealed a hemoglobin of 90 g/L and a test now showed repetitive late decelerations with a loss of baseline variability. Immediate ultrasonography done by the attending obstetrician demonstrated free fluid in the upper abdomen with a vaguely outlined mass in the left upper quadrant. The uterus appeared intact. Fetal tone was reduced and no body movements were observed. Intraperitoneal hemorrhage, likely secondary to splenic artery aneurysm with resulting fetal distress, was diagnosed.

Immediate laparotomy for a cesarean section was performed and a general surgeon was called urgently for definitive surgery. On entering the abdomen, approximately 1500 ml of free blood was found as well as a massive hematoma obscuring the entire left upper quadrant. A standard cesarean delivery was made of a 2240-g female infant who had an Apgar score of 3 and 5 at 1 and 5 minutes respectively.

Intraperitoneal bleeding was massive and required aortic compression before splenectomy and distal pancreatectomy could be accomplished. The patient's condition on completion of surgery was stable. She was discharged 13 days

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postoperatively. The infant required a longer hospitalization because of her prematurity.

Pathological examination showed a splenic artery aneurysm.

Discussion

Nearly 100 ruptured splenic artery aneurysms in pregnancy have been reported. The outlook for mother and fetus apparently continues to be poor. A relatively recent case report of maternal death from this condition would suggest that the passage of time, improvements in antenatal care and technologic advances have not reduced the likelihood of a poor result. "The diagnosis depends ultimately on thinking of the condition."[2]

The differential diagnosis after initial assessment usually includes abruptio placentae or a ruptured uterus even though neither history nor physical examination suggests that either of these entities are present. Early operation with cesarean section does not guarantee a definitive diagnosis, and subsequent maternal deaths have been reported.[3]

Previous exposure to a similar case led the obstetrician involved in this case to perform the ultrasonography, which confirmed his clinical impression. The presence of a general surgeon and immediate definitive surgery at the time of cesarean section undoubtedly contributed to reduced blood loss and the survival of both mother and fetus.

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Use in Pregnancy

The safety of MEFOXIN® in the treatment of infections during pregnancy has not been established. If the administration of MEFOXIN® to pregnant patients is considered necessary, its use requires that the anticipated benefits be weighed against possible hazards to the fetus. Reproductive and teratogenic studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the fetus due to MEFOXIN®.

Nursing Mothers

Cefoxitin is excreted in human milk.

Children

In children 3 months of age or older, higher doses of MEFOXIN® (100 mg/kg/day and above) have been associated with an increased incidence of eosinophilia and elevated SGOT.

ADVERSE REACTIONS

MEFOXIN® is generally well tolerated. Adverse reactions rarely required cessation of treatment and usually have been mild and transient.

Local Reactions
Thrombophlebitis has occurred with intravenous administration. Some degree of pain and tenderness is usually experienced after intramuscular injections using water. Induration has occasionally been reported.

Allergic
Maculopapular rash, urticaria, pruritus, eosinophilia, fever and other allergic reactions have been noted.

Gastrointestinal
Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Blood
Eosinophilia, leukopenia, neutropenia, hemolytic anemia, and thrombocytopenia and bone marrow depression have been reported. Some individuals, particularly those with azotemia, may develop positive direct Coombs tests during therapy with MEFOXIN®.

Liver Function
Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase and jaundice have been reported.

Cardiovascular Function
Hypotension.

Renal Function
Elevations in serum creatinine and/or blood urea nitrogen levels have been observed. As with the cephalosporins, acute renal failure has been reported rarely. The role of MEFOXIN® in changes in renal function tests is difficult to assess, since factors predisposing to prerenal azotemia or to impaired renal function have often been present.

TREATMENT OF OVERDOSE

Other than general supportive treatment, no specific antidote is known. MEFOXIN® can be eliminated by dialysis in patients with renal insufficiency.

DOSAGE AND ADMINISTRATION

MEFOXIN® may be administered intravenously or intramuscularly as required. (See complete monograph on ADMINISTRATION and RECONSTITUTION.)

Intravenous Administration
The intravenous route is preferable for patients with bacteremia, bacterial septicemia, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.

TREATMENT DOSAGE

Adults

The usual adult dosage is 1 g or 2 g of MEFOXIN® every 6 to 8 hours. Dosage and route of administration should be determined by severity of infection, susceptibility of the causative organisms, and condition of the patient. The usual adult dosages are shown in the Table below.

Usual Adult Dosage

Type of infection	Daily Dosage	Frequency and Route
Uncomplicated forms* of infections such as pneumonia, urinary tract infection, soft tissue infection	3-4 g	1 g every 6-8 h I.V. or I.M.
Moderately severe or severe infections	6-8 g	1 g every 4 h or 2 g every 6-8 h I.V.
Infections commonly needing antibiotics in higher dosage (e.g. gas gangrene)	12 g	2 g every 4 h or 3 g every 6 h I.V.

*Including patients in whom bacteremia is absent or unlikely

Therapy may be started while awaiting the results of susceptibility testing.

Antibiotic therapy for group A beta-hemolytic streptococcal infections should be maintained for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated.

Adults with Impaired Renal Function

MEFOXIN® may be used in patients with reduced renal function but a reduced dosage should be employed and it is advisable to monitor serum levels in patients with severe impairment.

In adults with renal insufficiency, an initial loading dose of 1 g to 2 g should be given. After a loading dose, the following recommendations for **maintenance dosage** may be used as a guide:

MAINTENANCE DOSAGE OF MEFOXIN® IN ADULTS WITH REDUCED RENAL FUNCTION

RENAL FUNCTION	CREATININE CLEARANCE mL/min	DOSE	FREQUENCY
Mild impairment	50-30	1-2 g	every 8-12 h
Moderate impairment	29-10	1-2 g	every 12-24 h
Severe impairment	9-5	0.5-1 g	every 12-24 h
Essentially no function	<5	0.5-1 g	every 24-48 h

In patients undergoing hemodialysis, the loading dose of 1 - 2 g should be given after each hemodialysis, and the maintenance dose should be given as indicated in the Table above.

Neonates (Including Premature Infants), Infants and Children (See WARNINGS for Neonates under ADMINISTRATION in the complete monograph.)

Premature Infants with Body Weights Above 1500 g	20-40 mg/kg every 12 h I.V.
Neonates	
0-1 week of age	20-40 mg/kg every 12 h I.V.
1-4 weeks of age	20-40 mg/kg every 8 h I.V.
Infants	
1 month to 2 years of age	20-40 mg/kg every 6 h or every 8 h I.M. or I.V.
Children	20-40 mg/kg every 6 h or every 8 h I.M. or I.V.

In severe infections, the total daily dosage in infants and children may be increased to 200 mg/kg, but not to exceed 12 g per day.

MEFOXIN® is not recommended for the therapy of meningitis. If meningitis is suspected, an appropriate antibiotic should be used.

At present there is insufficient data to recommend a specific dosage for children with impaired renal function. However, if the administration of MEFOXIN® is deemed to be essential the dosage should be modified consistent with the recommendations for adults (see Table above).

PROPHYLACTIC USE

For prophylactic use, a three-dose regimen of MEFOXIN® is recommended as follows:

Vaginal or abdominal hysterectomy and abdominal surgery

2 g administered intramuscularly or intravenously just prior to surgery (approximately one-half to one hour before initial incision).

The second and third 2 g doses should be administered at 2-6 hour intervals after the initial dose.

Cesarean Section

The first dose of 2 g should be administered intravenously as soon as the umbilical cord has been clamped. The second and third 2 g doses should be given intravenously or intramuscularly four hours and eight hours after the first dose.

AVAILABILITY

MEFOXIN® is supplied as sterile powder in boxes of 10 vials:

3356 Ca - 1 g cefoxitin as sodium salt
3357 Ca - 2 g cefoxitin as sodium salt

Storage
MEFOXIN® in the dry state should be stored below 30°C. The dry material as well as solutions tends to darken, depending on storage conditions; product potency, however, is not adversely affected.

PRODUCT MONOGRAPH AVAILABLE ON REQUEST

(332-a,4,89)

3386

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Cholesterol Granuloma of the Peritoneum

A.F. Al-Amer, MB, FRCS;* H.S. Walia, MB, MS, FRCS(Edin), FRCS;* J.P. Madda, MRCPath†

Cholesterol granulomas are common in the mastoid region but have rarely been reported in other areas. The authors report the case of a 40-year-old man who had a cholesterol granuloma of the peritoneum. They discuss the morphology of the condition and the difficulties of diagnosis. It is likely that chronic or recurrent inflammation plays a major role in the pathogenesis and that, when dealing with such lesions preoperatively or intraoperatively, a radical approach may not be necessary.

Les granulomes de cholestérol sont fréquemment observés dans la région mastoïdienne mais ils ont rarement été signalés dans d'autres régions. Les auteurs décrivent le cas d'un homme de 40 ans présentant un granulome de cholestérol dans le péritoine. Ils commentent la morphologie de ce granulome et les difficultés de diagnostic. Il est vraisemblable qu'une inflammation chronique ou récurrente joue un rôle important dans sa pathogénèse et que, face à une telle lésion, avant ou durant une intervention chirurgicale, une approche radicale ne soit pas nécessaire.

Cholesterol granuloma is essentially a foreign-body reaction in response to cholesterol crystals.[1] This is a well-defined entity in the otology literature but has rarely been reported in other areas.[2-4] The biologic benignity of the lesion is well established; a few studies have recorded its destructive character.[4,5] The lesion often simulates malignant disease in the abdomen[6,7] and has posed a problem for both pathologists and surgeons.

This report describes the occurrence and morphogenesis of an unusual form of an intra-abdominal lesion and the difficulties in establishing its diagnosis.

Case Report

A 40-year-old Arab man gave a history of upper abdominal pain for 6 months and weight loss of 7 kg in the previous 3 months in spite of having a normal appetite. The pain was colicky, moderate to severe, lasting a few minutes to 90 minutes, radiating to the back and not accompanied by nausea or vomiting. There was no history of hematemesis, melena or jaundice. The patient was a nonsmoker, consumed a moderate amount of alcohol and was known to have glucose-6-phosphate dehydrogenase deficiency.

Examination revealed a healthy-looking patient with no cyanosis, jaundice or pallor. There was no lymphadenopathy and the thyroid and pulses were normal. Systemic physical examination revealed no abnormality and the abdominal examination gave normal findings, apart from mild tenderness in the epigastrium.

Laboratory investigations showed a hemoglobin value of 111.1 g/L and an erythrocyte sedimentation rate of 14 mm/h. Hematologic indices indicated hypochromic microcytic anemia. The biochemical profile revealed a serum iron level of 12.1 μmol/L (normal 14 to 31 μmol/L) and a total iron-binding capacity of 4.8 g/L (normal 2.5 to 4.2 g/L), but the rest of the profile was normal. Serum amylase concentration was 103 U/L (normal up to 85 U/L). Upper gastrointestinal endoscopy showed only a deformed bulb. Computed tomography scanning showed that the head of the pancreas was swollen and edematous, the wall of the second part of the duodenum was thickened and the lower end of the common bile duct was slightly dilated. The patient did not appear for the scheduled endoscopic retrograde cholangiopancreatography (ERCP). Routine urinalysis and stool culture examination, x-ray films of the chest and abdomen and ultrasonography gave normal results.

The patient returned with similar complaints 2 months later. Repeat ultrasonography showed a 6 × 3 cm cystic mass in the head of the pancreas, suggesting a pseudopancreatic cyst. Computed tomography suggested a mass, likely cystic, but could not eliminate a fluid collection or a malignant lesion. Repeat endoscopy showed a polypoid mass 1 cm above the ampulla of Vater, highly suggestive of a periampullary carcinoma. Biopsies were taken, but only inflammatory tissue was found. Endoscopic retrograde cholangiopancreatography revealed normal common bile, pancreatic and cystic ducts and gallbladder. Barium meal examination and hypotonic duodenography suggested a thickened and rigid second part of the duodenum with destroyed or irregular mucosa, highly suggestive

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of a malignant condition. In view of these findings a presumptive diagnosis of ampullary carcinoma was made.

At operation through a long midline incision, a mass 5 × 6 cm involving the head of the pancreas and second part of the duodenum was seen. There were 1- to 2-mm seedlings, transparent to pearl white, involving most of the upper abdomen (i.e., peritoneum and liver surfaces). There were heaped masses of these in the subphrenic recesses and a few scattered over the small bowel and peritoneum of the lower abdomen. A duodenotomy revealed a 3 × 4 cm ulcerated lesion with a fistulous track leading into the head of the pancreas. It was our opinion that the head of the pancreas was carcinomatous with secondary lesions. Biopsies were taken from the ulcerated lesion inside the head of the pancreas, the peritoneum, surface of the liver and the heaped masses. Frozen section (Fig. 1) was interpreted as containing malignant tissue, possible from the pancreas, but this was subsequently shown to be incorrect.

On the basis of this report a bypass procedure, consisting of an antecolic gastrojejunostomy, cholecystojejunostomy and jejunojejunostomy was carried out. The patient's postoperative course was uncomplicated. On postoperative day 10, the revised diagnosis was received with surprise.

Pathological Findings

Paraffin sections (Fig. 2) from the liver and peritoneum revealed the true nature of the lesions. They showed multinucleated giant cells encircling cholesterol crystals in some areas of fat tissue. Empty clefts were also seen in the fibrotic areas of the fat tissue.

The tears within the tissue on frozen section contributed to the error in histologic interpretation. They imparted an appearance similar to epithelial lining, a papillary structure. The dissolution of cholesterol crystals during staining of the frozen section gave spaces completely surrounded by multinucleate cells a duct-like appearance. The lack of basement membrane to the ductular epithelium, so formed, tilted the diagnosis in favour of adenocarcinoma. After being fixed, the tissues are firmer and less likely to be torn; thus, even if the crystals dissolved their shape could be inferred from tissue molds or clefts that are left behind.

The pancreatic biopsy showed marked periductal infiltration of lymphocytes and plasma cells, and

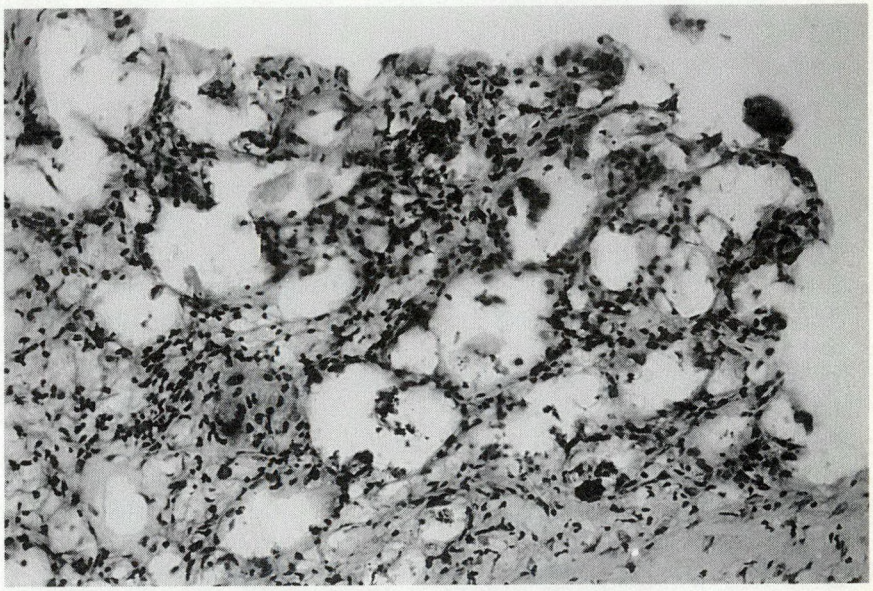

FIG. 1. Frozen section. Appearance of tissue from surface of liver. Note papillary structures formed as result of tissue tears caused by presence of cholesterol crystals (hematoxylin and eosin, original magnification × 400).

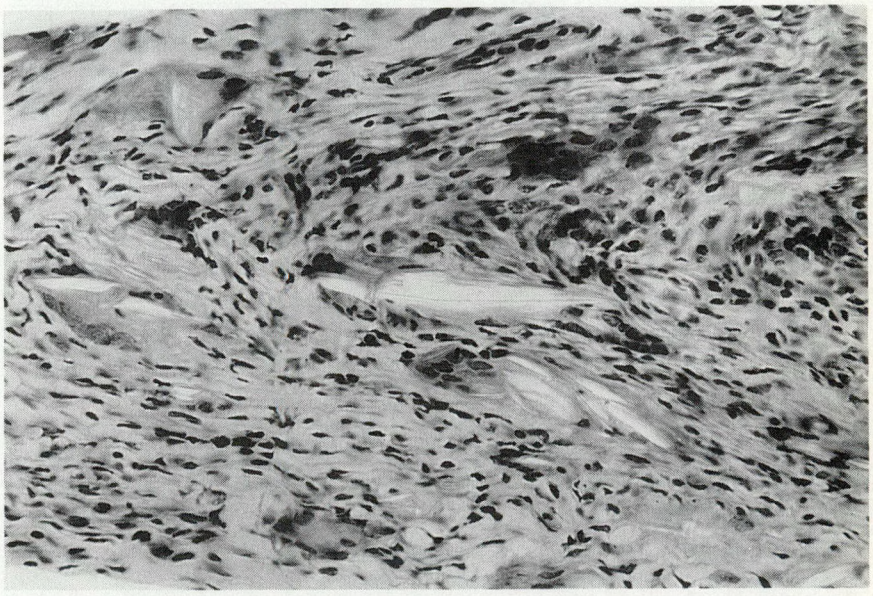

FIG. 2. Paraffin section. Cholesterol crystal (centre) is lying next to multinucleate foreign body giant cell (hematoxylin and eosin, original magnification × 400).

no luminal concretion was present. The acinar tissue showed a diffuse scattering of polymorphonuclear leukocytes together with numerous lymphocytes and plasma cells. No acinar tissue necrosis or atrophy was seen. No fibrosis or calcification was present. The islets were normal.

The final diagnosis was cholesterol granulomas of the peritoneum and liver, with active chronic pancreatitis. Clearly the patient had had a pseudocyst in the head of the pancreas which had ruptured into the duodenum and drained before surgery.

Follow-up

At follow-up, 2 months after operation, the patient was completely free of pain and had put on 10 kg in weight. Ultrasonography showed no abnormality and computed tomography revealed further regression of the lesion in the head of the pancreas.

The patient was admitted 4 months later with epigastric pain radiating to his back and with occasional vomiting. He had resumed drinking alcohol, half a bottle a day. Clinical examination gave normal results. However, the serum amylase level ranged from 136 to 150 U/L (normal less than 85 U/L) and the 24-hour urinary amylase level was also elevated to 140 U/L (normal 4 to 37 U/L). Roentgenography of the abdomen, ultrasonography, gallium scanning and ERCP gave normal results, but the computed tomography scan showed persistence of a small cystic lesion, less than 1 cm in dimension in the head of the pancreas. Endoscopy revealed the presence of a fistulous tract above the ampulla. Biopsies taken from the area showed only an inflammatory reaction. The patient fitted into a pattern of established chronic pancreatitis. So far no evidence of malignancy has been found. On further follow-up 9 months later, repeat endoscopy revealed the persistence of a fistulous tract, but it was smaller. The patient still complained of pain, for which analgesics were prescribed, and he was advised to avoid alcohol consumption.

Discussion

The cholesterol granuloma is a known entity in otology, usually found in the mastoid region and mostly associated with chronic otitis media and cholesteatoma. Rarely has this lesion been reported in the thyroglossal duct,[2] parotid gland,[3] lymph nodes,[7] kidneys,[8] liver,[9] or spleen.[9] It has never been reported before in the peritoneum.

Granulomatous inflammation is a common tissue response to a variety of stimuli, including lipids, which may come from exogenous[10] or endogenous[11] sources. Rubinstein and Brenner[9] coined the term lipogranulomatosis in preference to pseudosarcoid granuloma, because the etiology may not be known in some cases. Cholesterol granuloma is a specific histologic entity consisting of fibrous granulation tissue in which a large number of cholesterol crystals have been deposited and surrounded by foreign-body giant cells, a condition that requires careful differentiation from tuberculosis[12] and sarcoidosis.[13] The cholesterol, according to Friedman,[1] comes from the breakdown of blood. Sade and Teitz[14] suggested hypoxic breakdown of tissue, and Aviel and associates[2] mention tissue breakdown secondary to persistent inflammation as the possible source.

There is a paucity of reports of this condition in the literature; of the three case reports of abdominal lipogranulomatosis only one was of cholesterol granuloma.[7] The remaining two reports were cases of idiopathic lipogranulomatosis,[9] the etiology of which could not be established. Most of the reported cases were in Caucasians, whereas our patient is an Arab. The history of ingestion or injection of mineral oil or radiographic material is important. The age of reported cases ranged from 35 to 69 years. Patients usually present with abdominal pain and weight loss. Only one patient had night sweats. Cholesterol granuloma is often associated with cholesterol-rich lesions, leakage of which would result in its ingestion by macrophages, causing organomegaly and lymphadenopathy. Usually the diagnosis is an incidental histologic finding. These features are unhelpful since they could be compatible with any of the principal differential diagnoses. Special investigations like barium meal examination, ultrasonography, computed tomography, angiography or ERCP may not reveal the diagnosis. A quick section may not be helpful because dissolution of cholesterol crystals during staining causes spaces surrounded by multinucleate cells, which have a duct-like appearance and can be misinterpeted as carcinoma as in our case. Thus there is no one test except histologic examination of paraffin sections that clearly separates cholesterol granuloma from its chief differential diagnoses.

Our case of cholesterol granuloma in the peritoneum appears to be the only case of its kind in the English literature. Morphogenesis appears to be secondary to erosion, leak and fistulization of the duodenum by a pseudopancreatic cyst, thus evacuating itself. Pseudocysts are known to contain a mixture of necrotic debris, blood and enzyme which subsequently becomes liquified and has the propensity to leak,

erode or rupture. This seems to have happened in our case, in which release of this fluid, rich in cholesterol, elicited a mononuclear phagocytic and foreign-body granulomatous reaction, resulting in formation of miliary seedlings across the upper abdomen, with heaping of collections of these lesions in the subphrenic spaces. This diagnosis must be differentiated from peritoneal tuberculosis, starch granuloma and metastasis from stomach, pancreas and ovaries.

In theory no treatment is required. However, all the tissue is invariably removed at the time of the surgical procedure when malignancy is suspected or some lesser procedure is done. If the diagnosis is entertained, pre- or intraoperatively, when dealing with such lesions, a radical approach may not be necessary. Frozen section in such cases may help in reaching the correct diagnosis, provided the pathologist is aware of the possibility.

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SESAP VI Critique

Item 24

The pathogenesis of peptic ulcer disease is multifactorial. Some patients with peptic ulcer have an increased parietal cell mass, which results in acid hypersecretion. Others have increased serum levels of gastrin or an increased parietal cell sensitivity to gastrin. Another subgroup is believed to have enhanced vagal tone, which increases parietal cell sensitivity to gastrin and the parietal cell mass. The hormone somatostatin may serve as a regulator of acid secretion. Therefore, reduced somatostatin could be part of the pathogenesis of ulcer disease. However, somatostatin has not been consistently found to be decreased in patients with ulcers. Gastric mucosal production of prostacyclin (PGI_2) is either normal or reduced in ulcer patients. Although some of the prostaglandins may have a cytoprotective effect, prostacyclin has not been shown to have any effect on ulcer disease.

E

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Prescribing Information

ACTION

ERGAMISOL (levamisole hydrochloride) is capable of restoring impaired immune responses preferentially of the cell mediated type in compromised hosts. Therapeutic doses of levamisole restore to normal the functions of monocytes (phagocytes) and T lymphocytes but do not directly influence B cells.

Levamisole is rapidly absorbed from the gastrointestinal tract following a single oral ingestion of 150 mg. In patients with neoplastic disease, a mean peak blood level of 0.86 mcg/mL is attained within 2 hours of intake.

The half-life of elimination of levamisole alone is between 3-4 hours. The metabolites are eliminated more slowly with a terminal half-life of approximately 16 hours. Levamisole is extensively metabolized by the liver in man and excreted mainly by the kidneys (70% over 3 days). Approximately 5% is excreted in the feces. Less than 5% of the unchanged dose is excreted in the urine and less than 0.2% in the feces.

INDICATIONS

ERGAMISOL (levamisole hydrochloride) is indicated as adjuvant therapy in poor prognosis malignant melanoma following complete surgical excision and exclusion of metastatic disease. In such patients, levamisole has been shown to produce an improvement in relapse free survival and overall survival when compared to observation alone, particularly in patients aged 55 years or older.

ERGAMISOL is also indicated as adjuvant therapy, in combination with 5-fluorouracil, in patients with completely resected Dukes' stage C colon cancer. Evidence of metastatic disease must be excluded before initiating therapy. In patients with Dukes' stage C carcinoma of the colon, a regimen of levamisole plus 5-fluorouracil has been shown to produce significant reductions in both cancer recurrence and overall death rate.

CONTRAINDICATIONS

Levamisole is contraindicated in patients with a known hypersensitivity to the drug.

WARNINGS

ERGAMISOL (levamisole hydrochloride) has been associated with reversible leukopenia and agranulocytosis, therefore it is essential that appropriate hematological monitoring be done routinely during therapy with ERGAMISOL.

Patients should be instructed to report immediately any sudden change in their state of health which may be manifested by influenza-like symptoms (fever, lassitude, sore throat, shivering or sweating) so that appropriate hematological testing can be done.

Leukopenia (total WBC below 3000 mm^3) is not necessarily a sign of impending agranulocytosis; recovery is possible without withdrawal of the drug. However, with a reduced neutrophil count (less than 20% of the total white blood cell count) levamisole should be discontinued permanently. (Agranulocytosis is attributed to antibody formation and absorption of immune complexes. This process initiates complement activation and cell lysis; levamisole itself does not directly damage granulopoiesis.)

The HLA genotype B27 predisposes to the development of agranulocytosis, particularly in females with concomitant rheumatoid arthritis. The onset is frequently sudden and may be asymptomatic. Following discontinuation of levamisole, neutrophil counts normalize within a week to 10 days. There is no evidence that steroids or WBC transfusions are of significant therapeutic value; prophylaxis of infection during the acute phase of agranulocytosis should be an important consideration.

PRECAUTIONS

Drug Interactions: The therapeutic effect of levamisole may be antagonized by concomitant administration of corticosteroids.

Additional caution is necessary when levamisole is used in combination with other drugs potentially affecting hemopoiesis.

Levamisole has been reported to produce "ANTABUSE™"-like side effects when given concomitantly with alcohol.

ADVERSE REACTIONS

Approximately half of all patients treated with ERGAMISOL (levamisole hydrochloride) experience adverse effects of the medication. Due to the intermittent nature of the dosage schedule, drug discontinuation may not be necessary for successful resolution.

The adverse reactions observed when levamisole is used in combination with 5-fluorouracil are consistent with those anticipated if 5-fluorouracil is given alone in a comparable dose and schedule.

The incidence of adverse reactions for levamisole alone in malignant melanoma patients and for levamisole plus 5-fluorouracil in colonic cancer patients is presented in the following table:

	INCIDENCE (%)		
	LEVAMISOLE	LEVAMISOLE+5-FU	
		COLONIC	
ADVERSE REACTIONS	MELA-NOMA	INDUC-TION	MAINTE-NANCE
GASTROINTESTINAL			
nausea	24	37	56
vomiting	6	8	17
diarrhea		25	47
taste change	10	2	7
anorexia	1		
MUCOCUTANEOUS			
stomatitis	1	27	28
dermatitis	4	8	22
severe		1	1
alopecia		4	22
conjunctivitis		1	7
hyperpigmentation			2
HEMATOLOGICAL			
leukopenia	10		
2000 to 4000/mm^3		38	38
less than 2000/mm^3		7	2
thrombocytopenia			
50000 to 130000 /mm^3		4	18
less than 50000 /mm^3		2	4
agranulocytosis	1.4		
MUSCULOSKELETAL			
arthralgia/myalgia	8	2	4
NEUROLOGIC			
visual change			2
smell change		1	2
headache		1	5
dizziness/vertigo		1	4
ataxia			3
anxiety/irritability		2	2
depression		1	2
insomnia			1
somnolence			1
impaired thinking		1	2
OTHER			
fatigue/weakness		5	11
fever	8		
impaired liver function		1	2

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no experience of overdosage with ERGAMISOL (levamisole hydrochloride). At high doses ERGAMISOL exhibits positive inotropic and chronotropic properties on heart muscle as well as convulsant properties. General supportive measures are recommended.

DOSAGE AND ADMINISTRATION

In patients with malignant melanoma

ERGAMISOL (levamisole hydrochloride) should be administered at a dose of 2.5 mg/kg given as a single daily dose, preferably at night, on 2 consecutive days every week. Higher doses are not recommended as they are associated with increased toxicity and have not been shown to provide any additional therapeutic benefit.

In patients with Dukes' stage C carcinoma of the colon

Levamisole plus 5-fluorouracil should be administered only by or under the supervision of qualified physicians, experienced in cancer chemotherapy, and well versed in the use of potent antimetabolites.

Therapy with ERGAMISOL may be initiated as soon after resection as patients are able to tolerate oral medication, but no sooner than one week and no later than five weeks after surgery.

ERGAMISOL should be administered orally at a dose of 50 mg t.i.d., for three consecutive days, every two weeks. This therapy should be continued for at least one year.

Administration of 5-fluorouracil should be timed to begin concomitantly with the second three day course of levamisole. The initial dosage of 5-fluorouracil should be 450 mg/m^2/day, given intravenously, for five consecutive days.

Four weeks following the initial five day course of 5-fluorouracil, patients should begin maintenance therapy on a once weekly basis with an intravenous injection of 5-fluorouracil at a dose of 450 mg/m^2. Treatment should continue for as long as levamisole is administered.

If the patient experiences stomatitis, diarrhea or leukopenia, the weekly 5-fluorouracil administrations should be deferred until these side effects have subsided. If these side effects are moderate to severe in intensity, 5-fluorouracil should be resumed with a 20% reduction in the dose.

Dosage Forms:

Availability: ERGAMISOL tablets 50 mg are available in blister packages of 36 tablets.

Storage: ERGAMISOL tablets 50 mg should be stored at room temperature and protected from moisture and light.

Product monograph available on request.

1. Moertel CG et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *New Engl J Med.* 1990;322:352–8.

Imipenem Versus Tobramycin-Antianaerobe Antibiotic Therapy in Intra-abdominal Infections

Dan Poenaru, MD; Mary De Santis, RN; Nicolas V. Christou, MD, PhD

The authors compared broad-spectrum monotherapy with imipenem to an aminoglycoside-based antibiotic regimen for the management of intra-abdominal infections. One hundred and four patients who had intra-abdominal infection were randomly allocated to receive imipenem (52) or tobramycin plus clindamycin or metronidazole (52). Patients treated with imipenem had fewer febrile episodes and occurrences of breakthrough bacteremia, less antibiotic resistance and need for drug change; their hospital stay was shorter. The death rate from sepsis was 4% in patients who received imipenem and 13% in those who received the combined regimen ($p = 0.08$). Treatment was successful in 79% of patients on imipenem versus 67% of those receiving an aminoglycoside. Patient stratification by the APACHE II system and probability of death calculation using delayed-type hypersensitivity scores predicted a similar death rate for the two treatment groups. Imipenem appears to be a safe and efficacious alternative broad-spectrum antibiotic for treating patients who are seriously ill with intra-abdominal infection.

Les auteurs ont comparé l'imipénem en monothérapie à large spectre, à une antibiothérapie renfermant un aminoside dans le traitement des infections intra-abdominales. Cent quatre patients souffrant d'infections intra-abdominales ont été assignés de façon aléatoire à recevoir de l'imipénem (52) ou de la tobramycine associée à la clindamycine ou au métronidazole (52). Les patients qui reçurent l'imipénem présentèrent moins de poussées fébriles, de bactérémies, de résistance aux antibiotiques et nécessitèrent moins de changements de médications; leur séjour hospitalier fut plus court. La mortalité due aux sepsies fut de 4% chez les patients qui reçurent l'imipénem et de 13% pour ceux qui reçurent le traitement d'association ($p = 0.08$). Une guérison fut enregistrée chez 79% des patients traités à l'imipénem par rapport à 67% chez ceux qui reçurent un aminoside. La stratification des patients selon le système APACHE II et la probabilité de décès calculée à l'aide de cotes d'hypersensibilité retardée laissaient prévoir un taux de mortalité similaire dans les deux groupes. L'imipénem semble être une alternative sûre et efficace dans l'antibiothérapie à large spectre des infections intra-abdominales graves.

Intra-abdominal infection is a serious surgical problem associated with high morbidity and mortality.[1] Its management includes surgical débridement and drainage of abscesses as well as the administration of antibiotics. The bacteriologic findings often include facultative gram-negative and anaerobic organisms, with the anaerobes predominating.[2] It has become common practice to treat both of these components, despite relatively weak support for such an approach.[1] The mainstay of pharmacotherapy in intra-abdominal infection has hence become an aminoglycoside to treat the gram-negative organisms in combination with either clindamycin or metronidazole for the anaerobes. The well-known adverse effects associated with aminoglycoside use, such as ototoxicity and nephrotoxicity, have led to a search for alternatives to the aminoglycoside-based regimen. Several second- and third-generation cephalosporins have been suggested as being equivalent to the combined therapy.[3-5] The emergence of β-lactamase-mediated bacterial resistance to these agents[6] has prompted the development of newer antimicrobials, such as the carbapenems, monobactams and quinolones.

Imipenem is an amidine derivative of thienamycin, a β-lactam antibiotic produced by *Streptomyces cattleya*.[7] Because of the drug's rapid metabolism by the renal enzyme dehydropeptidase-I, it is administered with cilastatin, a specific inhibitor of the enzyme. The drug is not only resistant to β-lactamase, but is an efficient inhibitor of many such enzymes.[8] The in-vitro spectrum of imipenem is extremely wide, including most aerobic and anaerobic gram-negative and gram-positive bacteria; at concentrations of 8 mg/L the drug inhibits over 98% of clinically important pathogenic species.[9] The only notable

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exceptions to imipenem's coverage are *Xanthomonas (Pseudomonas) maltophilia, Pseudomonas cepacia, Streptococcus faecium, Chlamydia trachomatis* and *Flavobacterium* spp.[10]

The clinical efficacy of imipenem has been tested in several randomized comparative trials, both against aminoglycoside-based regimens[11-14] and cephalosporins.[15,16] However, few investigators have specifically evaluated the drug in intra-abdominal infections.[12,17,18] The purpose of this prospective randomized study was to compare the efficacy and safety of imipenem with that of an aminoglycoside-based regimen in patients with intra-abdominal sepsis.

Patients and Methods

Patients admitted to the surgical wards or the surgical intensive care unit of the Royal Victoria Hospital in Montreal were entered prospectively into the trial. The study was approved by the departmental ethics reviews board. Included were patients admitted for emergency operation who were suspected, clinically, of having intra-abdominal infection on the basis of the history, physical examination and laboratory or radiographic findings. Those who had gynecologic and perianal infections, overt renal failure requiring dialysis, concomitant central nervous system infection and hypersensitivity to the study drug(s) or were pregnant were excluded as were patients suffering from uncomplicated acute cholecystitis, appendicitis without perforation, traumatic bowel perforation of less than 12 hours' duration or perforated peptic ulcers of less than 24 hours' duration. In our opinion the last four conditions primarily reflect an inflammatory process, not an infection. Shock, organ failure or advanced age were not reasons for exclusion.

Antimicrobial Therapy

After they had given their informed consent, the patients were randomly allocated to receive either imipenem/cilastatin (500 mg every 6 hours intravenously) or tobramycin plus anaerobic coverage. Tobramycin, 1.5 mg/kg intravenously every 8 hours, was given to patients whose renal function was normal. The dosage interval was adjusted according to the creatinine clearance rate in patients whose renal function was impaired. Serum tobramycin levels were measured before and after the fourth dose, and either dose or interval was adjusted to obtain peak drug levels between 6 and 10 μg/ml and trough levels not less than 1.5 μg/ml. Anaerobic coverage was provided with either clindamycin 600 mg every 6 hours or metronidazole 500 mg every 6 hours, both administered intravenously, depending on the origin of the infection and the treating physician's preference. Treatment was continued until there was clinical evidence that the infection had resolved or that a change of antibiotic was required.

Data Collection

Upon entry into the study, a clinical history was obtained and physical examination performed. Changing physical signs and symptoms, as well as daily temperature charts, were recorded throughout the trial. Laboratory data collected included the results of hematologic and biochemical screening and urinalysis, performed on admission and every 3 days during the study. The APACHE II score as devised by Knaus and colleagues[19] was calculated on admission, using the intensive care research unit APACHE II scoring sheets. Delayed-type hypersensitivity (DTH) skin testing was performed with five common recall antigens and the skin-test score calculated as described previously.[20] Calculation of the risk of death was estimated from formulas and methodologies previously described.[19,20]

Microbiologic Evaluation

Upon admission, each patient had two sets of aerobic and anaerobic blood cultures done, as well as cultures of all suspected infection sites. Gram's staining of all specimens was performed routinely. Susceptibility to the study antibiotics and to other common antimicrobials was tested for by the FDA Standardized Disk Technique.[21]

Outcome

Outcome was evaluated by two methods. The local infection outcome was reported using the criteria of Solomkin and others.[1] A successful outcome required resolution of the infection without additional antibiotics. Failure was reported when: (a) lack of objective response to therapy necessitated a change in antibiotics or additional operations; (b) the original infection recurred at a site related to the initial infection; (c) a change of antibiotics was necessitated by an adverse reaction, a delayed response or in-vitro resistance of an isolate; (d) death occurred within a period related to the infectious episode and infection was a contributing factor. Outcome was indeterminate in cases of: (a) inadequate surgical procedures; (b) death associated with noncontributory infection or within 72 hours of initiation of therapy; (c) superinfection at the initial site, with organisms not identified at the onset of therapy.

The hospital outcome was recorded as alive, dead from sepsis,

and dead from causes other than sepsis. Death was considered septic related if uncontrolled infection was present at the time of death and no other independent causative factors could entirely account for the outcome.

Statistical Analysis

Differences between the groups were analysed using Student's two-sample *t*-test. The α and β limits of significant probability were set at 0.05 and 0.1, respectively. Probabilities of death in each group were calculated using the logistic regression formula of Knaus and associates[19] as well as an alternative formula using both APACHE II and DTH skin-test scores recently reported.[22]

Findings

Between September 1985 and October 1988, 104 patients were entered into the study; 52 patients received imipenem/cilastatin and 52 a combined aminoglycoside-based regimen (32 tobramycin and clindamycin and 20 tobramycin and metronidazole). Some of the admission parameters for each treatment arm are shown in Table I. The severity of illness (i.e., the septic response to infection in the two groups) was further estimated by the APACHE II score and by calculating the probability of death for patients receiving either regimen. None of these parameters showed statistically significant differences between the two groups.

Table II characterizes the various infections by type (e.g., peritonitis, intra-abdominal abscess) and by site of origin. Again the differences were not significantly different. The six patients who were classified as having neither peritonitis nor intra-abdominal abscess included three who had diverticulitis, one who had ulcerative colitis and one with a bilocutaneous fistula. The breakdown of pathogens into the three major classes in each type of infection is depicted in Fig. 1, and according to the site of infection in Fig. 2. There were no significant differences in the microbiologic findings in the two groups.

Table III sets forth the microbial resistance to the four antibiotics used. Listed are all the resistant strains that were encountered, both before and during the study. Those pathogens that were only partially characterized are included under the general class to which they belong. From the pathogens identified upon entry to the study anaerobes showed higher resistance, primarily to *Bacteroides fragilis* (three strains resistant to metronidazole, one to clindamycin), followed by *Clostridium* spp. There were no initial strains resistant to imipenem. A substantial number of gram-positive aerobes were resis-

Table I. Comparison of Admission Parameters in the Two Treatment Groups*

Variable	Imipenem (n = 52)	Combined treatment (n = 52)
Age, yr†	52.0 ± 17.3	57.6 ± 18.4
Sex		
Men	34	26
Women	18	26
Serum creatinine, g/L	100	105
Serum albumin, g/L†	31.6 ± 8.7	28.9 ± 6.1
Bacteremia pre-study, no. (%)	6 (12)	5 (10)
APACHE II score†	11.2 ± 9.1	13.1 ± 7.8
DTH score, mm†	12.3 ± 14.6	10.8 ± 18.6
Anergic, no. (%)	20 (38)	24 (46)
Probability of death		
by APACHE II	0.18	0.23
by APACHE II and DTH	0.14	0.20

*Differences were not significant.
†Values were mean ± standard deviation.

Table II. Distribution of Infections by Type and Site in the Two Treatment Groups

Site/type of infection	Imipenem no. (%) (n = 52)	Combined treatment no. (%) (n = 52)
Peritonitis	24 (46)	24 (46)
Intra-abdominal abscess	26 (50)	24 (46)
Other	2 (4)	4 (8)
Esophagus/stomach	6 (12)	7 (13)
Duodenum/small bowel	5 (10)	3 (6)
Colorectum	34 (65)	35 (67)
Pancreaticobiliary tract	7 (13)	6 (12)
Peritoneal cavity	0 (0)	1 (2)

tant to the combined regimen, while imipenem covered this bacterial class very well. During the therapy, resistant strains were identified in each treatment arm, with gram-positive aerobic strains encountered most frequently. Table IV shows the organisms and outcome for each treatment failure associated with pathogens resistant to the study drugs at the beginning of therapy. It can be seen that in the combined regimens both failures and deaths were encountered in patients harbouring resistant organisms.

Superinfections, defined as infections due to organisms resistant to the study drug, and their outcome are shown in Table V. Imipenem, partly due to its well-known resistance to *P. maltophilia,* contributes the same number of treatment failures as the combined regimens. As one would expect, superinfections in the combined regimens were caused chiefly by aerobic gram-positive pathogens which are not adequately covered.

In the combined regimens, tobramycin was given at a median dose of 80 mg every 8 hours (range from 60 mg to 180 mg), and the interval of administration ranged from 6 to 36 hours. In order to determine whether we achieved the targeted peak aminoglycoside concentration, we calculated both peak and trough tobramycin levels found at each sequential serum testing (Table VI). These showed a progressive increase in both peak and trough levels with each tobramycin serum check, approaching target levels. There was an inverse correlation between tobramycin serum levels and outcome.

Success of treatment was assessed in terms of both eradication of the infection (Fig. 3) and hospital outcome. There were more treatment successes and fewer failures and indeterminate outcomes in the imipenem group than in the aminoglycoside groups, but the differences were not significant. The effect of each treatment modality was assessed in terms of several parameters. Figure 4 shows the differences in five such measurements: occurrence of febrile episodes while on

Table III. Antimicrobial Resistance Patterns to Each Study Drug

	Before therapy		During therapy	
	Organism	**No.***	**Organism**	**No.***
Gram-positive aerobes				
Tobramycin	*Streptococcus* spp	4	*Streptococcus* spp	1
	Enterococcus	2	*Enterococcus*	2
			Staphylococcus epidermidis	2
			Staphylococcus aureus	1
Imipenem	None		*S. epidermidis*	4
			Corynebacterium	2
Gram-negative aerobes				
Tobramycin	None		None	
Imipenem	None		*Pseudomonas maltophilia*	2
Anaerobes				
Clindamycin	*Bacteroides fragilis*	1	None	
	Fusobacterium	1		
	AGPC	1		
Metronidazole	*B. fragilis*	3	AGPC	1
	Clostridium perfringens	1		
	AGPC	1		
Imipenem	None		AGPR	1

*Number of specimens encountered.
AGPC = anaerobic gram-positive cocci, AGPR = anaerobic gram-positive rods.

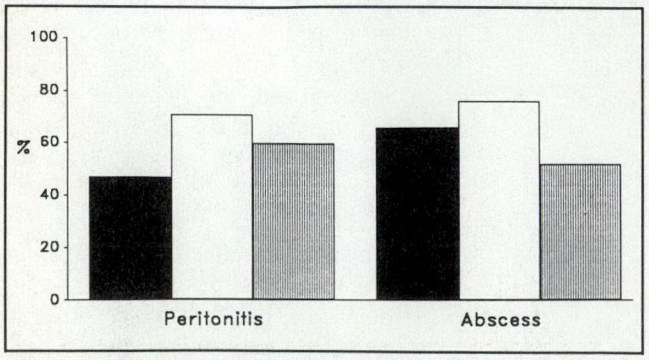

FIG. 1. Major bacterial classes encountered by type of infection. Black bars = gram-positive, white bars = gram-negative, dotted bars = anaerobes.

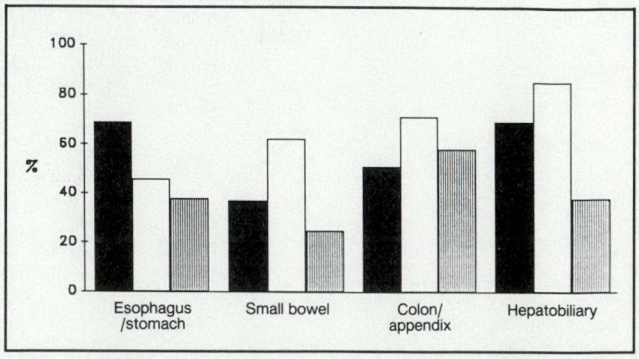

FIG. 2. Major bacterial classes encountered by source of infection. Black bars = gram-positive, white bars = gram-negative, dotted bars = anaerobes.

the study, occurrence of breakthrough bacteremias (i.e., bacteremias caused by pathogens that emerged during the therapy), resistance to the study antibiotic and need to change it, and length of hospital stay. Imipenem fared better than the combined regimens in every one of these respects, although only for the change in antibiotic was the difference significant ($p = 0.02$). Final hospital outcome is shown in Fig. 5. Although the percentage of imipenem-treated patients who died of their infection was lower than that for the combined regimens (4% versus 13%, $p = 0.08$), non-septic deaths in the two groups were similar.

The use of two different severity of disease scores has permitted the stratification of our patients and subsequent study of the effect of treatment in relation to illness severity in each subgroup. Figure 6 shows cumulative failures stratified according to the APACHE II score on admission, and in Fig. 7 the stratification is based on the individual probabilities of death derived from the APACHE II score and DTH logistic regression formula.[22] These two figures show the wide spectrum of distribution of patients according to the severity of their disease, as well as the differences in success between subgroups in the two treatment arms.

Only one adverse effect was encountered in our study, a transient tachycardia reported in the aminoglycoside group. We did not detect any change in serum creatinine levels after the study in these patients (pre-study mean serum creatinine was 105 g/L, post-study 112 g/L).

Table IV. Treatment Failures Associated With Pre-therapy Organisms Resistant to Study Drugs

Drug	Organism/no. specimens	Failed	Deaths
Imipenem	None	0	0
Tobramycin	*Streptococcus* spp (4)	2	2
	Enterococcus (2)	1	1
Clindamycin	*Bacteroides fragilis* (1)	0	0
	Fusobacterium (1)	1	1
	AGPC (1)	1	1
Metronidazole	*B. fragilis* (3)	2	0
	Clostridium perfringens (1)	0	0
	AGPC (1)	0	0

AGPC = anaerobic gram-positive cocci.

Table V. Treatment Failures Associated With Organisms Resistant to Study Drugs During Therapy ("Superinfections")

Drug	Organism	No.	Failed	Deaths
Imipenem	*Pseudomonas maltophilia*	2	1	1
	AGPR	1	0	0
	Staphylococcus epidermidis	4	1	0
	Corynebacterium	2	1	0
Tobramycin	AGPC	1	1	1
	S. epidermidis	1	0	0
	Enterococcus	1	1	0
Clindamycin	None	0	0	0
Metronidazole	AGPC	1	1	1

AGPC = anaerobic gram-positive cocci; AGPR = anaerobic gram-positive rods.

Table VI. Mean Tobramycin Serum Levels (g/ml)

	No.	Trough ± SEM	Peak ± SEM
First testing	48	1.52 ± 0.17	4.86 ± 0.25
Second testing	32	1.59 ± 0.19	5.80 ± 0.44
Third testing	11	2.05 ± 0.18	6.13 ± 0.41
Successful course	32	1.23 ± 0.16	4.41 ± 0.25
Failed course	11	1.83 ± 0.40*	5.43 ± 0.48*
*p (success versus failure).		p = 0.09	p = 0.05

Discussion

As concluded by Solomkin and colleagues[1] in their critical evaluation of antibiotic trials, studies evaluating therapy for intra-abdominal infections must demonstrate the following: inclusion of infections with high failure rates and sufficient numbers of patients, effective randomization techniques, stratification for other variables affecting outcome, precise outcome evaluation criteria and provision of sufficient data to support the outcome evaluation. In the design of our study we have attempted to follow these criteria, and our results generally reflect this.

The size of the population studied has always been a concern in trials of antibiotics, where small differences in drug efficacy require large numbers of patients for statistical significance. However, only a few reports on imipenem in the literature include more than 100 patients, and none of these have compared imipenem prospectively to conventional therapies in intra-abdominal infections. The largest study to date, that of Gonzenbach, Simmen and Angwerd,[18] included

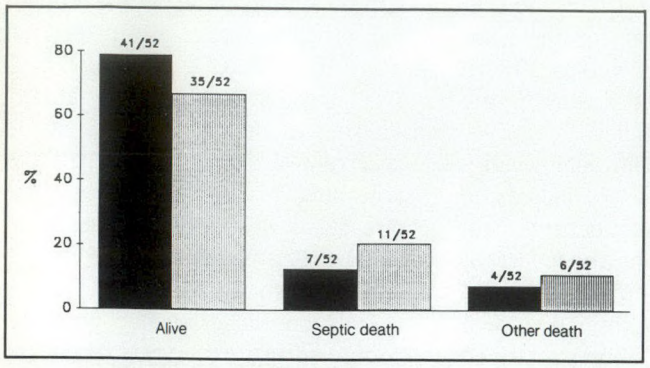

FIG. 3. Outcome in relation to local infection. Classification adapted from Solomkin and associates.[1] Black bars = imipenem, dotted bars = aminoglycoside.

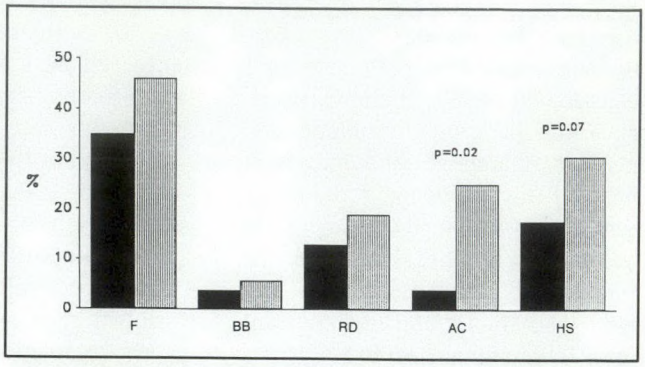

FIG. 4. Effect of antibiotic therapy on five study parameters: occurrence of febrile episodes while on study drug (F, body temperature greater than 38°C), occurrence of breakthrough bacteremias (BB), resistance to the study antibiotic (RD) and need to change it (AC), and length of hospital stay in days (HS). Black bars = imipenem, dotted bars = aminoglycoside.

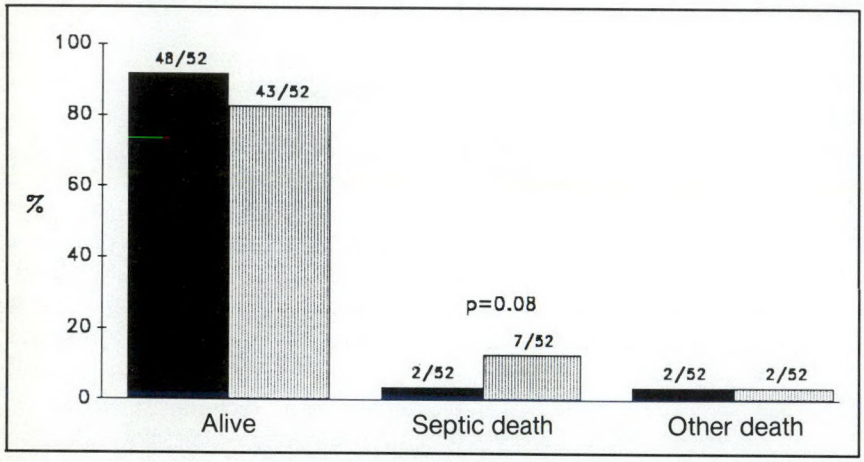

FIG. 5. Outcome in relation to final disposition for each treatment arm. Black bars = imipenem, dotted bars = aminoglycoside.

93 patients but provided no statistical analysis.

The admission parameters of our study revealed a seriously ill population with high APACHE II scores, high percentage of anergic and bacteremic cases and many patients classified as having major infections. We predicted overall mortalities in the order of 15% to 20% using our stratification formulas; the actual death rate was 13%.

In each of the parameters followed through the study, imipenem fared better than the combined aminoglycoside-based regimens. The differences in number of febrile episodes and length of hospital stay have been noted by others,[17,18] but we added such factors as the occurrence of breakthrough bacteremias, an initial resistance to the study antibiotic and the need to change the antibiotic. The last factor showed quite a striking effect: only 2 patients on imipenem needed to be switched to another antibiotic compared with 13 patients initially receiving an aminoglycoside-based regimen. This occurred because of bacterial resistance patterns combined with an unfavorable clinical impression, usually leading to the addition of a β-lactam antibiotic.

The pre-study resistance patterns support the existing evidence in favour of the extremely efficient antibacterial profile of imipenem.[8,9,23] With the exception of so-called "triple" regimens, which incorporate a β-lactam agent, aminoglycoside-based regimens cover gram-positive aerobes poorly. This was evidenced by the considerable number of resistant gram-positive strains, in keeping with the large proportion of this bacterial group in our infections. Besides, the substantial number of metronidazole-resistant *Bacteroides* strains was unsuspected and of concern.

When the resistant infections were related to eventual outcome, no treatment failure or death could be attributed to initial bacterial resistance to imipenem. Clindamycin and tobramycin, on the other hand, appeared commonly linked with resistance and subsequent failure. Five patients who had infections resistant to these drugs died. It is difficult to prove whether such associations are truly causal, but the patterns observed are nevertheless suggestive.

Superinfections with resistant organisms emerged during the treatment in two cases of *P. maltophilia* in our study; this represented 16% of all *Pseudomonas* strains. The refractoriness of *P. maltophilia* to

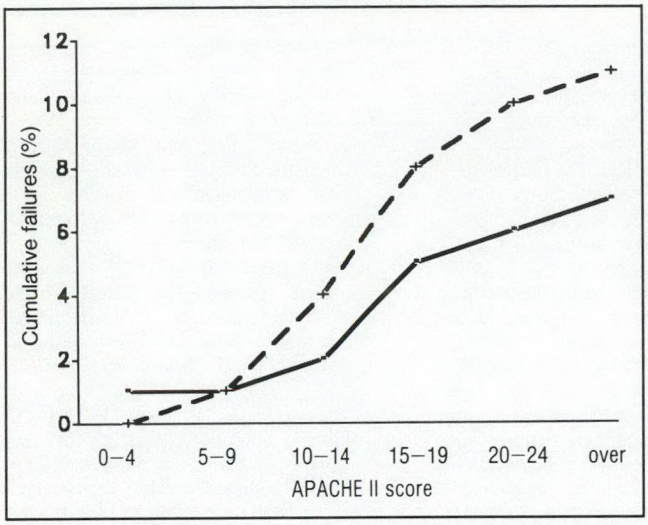

FIG. 6. Cumulative failures in each treatment group with patients stratified by APACHE II score. Solid line = imipenem, dotted line = combined regimen.

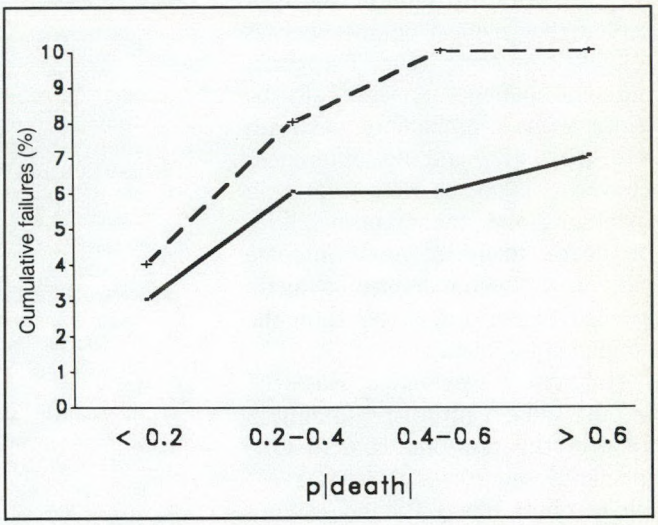

FIG. 7. Cumulative failures in each treatment group with patients stratified by death probability value (p/death/) derived from both APACHE II and DTH skin-test scores. Solid line = imipenem, dotted line = combined regimen.

imipenem may have been the cause of one treatment failure which eventually led to the patient's death. We did not, however, encounter any *Pseudomonas aeruginosa* resistant strains emerging during treatment, as recently shown by Calandra and associates.[24] On the other hand, there were three superinfections with aerobic gram-positive agents resistant to tobramycin, one in a patient who eventually died of sepsis. Hence, superinfections are a concern in traditional therapeutic regimens also, and their coverage with aminoglycosides is far from being adequate.

Measurement of aminoglycoside serum levels is essential for ensuring adequate treatment and for avoiding toxicity. During therapy we noted a constant need to change dosage and frequency of administration to achieve adequate tobramycin levels, rather than to avoid toxicity. Aminoglycoside treatment failures cannot be attributed to inadequate drug concentrations. Patients whose therapy failed had markedly higher peak and trough tobramycin levels than those with a successful outcome. Hence, careful aminoglycoside monitoring can optimize the antibiotic dosage without necessarily having prognostic value.

Although superiority of one antibiotic regimen over another requires comparison of many variables, clinical success and final hospital outcome remain the chief parameters. It is noteworthy that every trial of imipenem versus aminoglycoside-based combined regimens in intra-abdominal sepsis has shown improved outcome with imipenem, although none of the results have been statistically significant.[12,14,18,25] Our results clearly support this finding, and we were able, in the case of septic deaths, to approach statistical significance ($p = 0.08$). We had a considerable number of treatment failures and deaths in keeping with the relatively ill patient population that we studied. The use of an objective classification of outcome, as well as separate consideration of septic-related and non-septic deaths, enabled us to evaluate the antibiotic effect better. The overall medical condition of the patient remains, however, a major factor in the success of therapy; intra-abdominal infection is a surgical condition with a primarily surgical treatment strategy, and antibiotics remain an adjunctive therapy. Hence, we stratified our patients by severity of underlying condition in order to identify the subgroup most likely to benefit from the antibiotics. Stratification of the APACHE II scores revealed that "healthy" patients with scores less than 15 had few treatment failures and deaths regardless of the regimen used; the "sick" group with APACHE II scores over 15 was associated with most of the morbidity and mortality, and in this subgroup imipenem-treated patients tended to fare better. These data are in accord with the findings of Solomkin and colleagues.[14] The computation of actual probabilities of death for each patient allowed us to stratify our population by a comprehensive method that takes into account the state of the patients' host defence as well as physiological status, age and long-term health. Although hospital outcome would naturally be expected to worsen

with severity of disease, we observed that clinical course success followed the same trend. The good-outcome patients appeared to be those with a probability of death less than 0.2, and no differences between regimens were found in that subgroup; higher probabilities of death identified poor-outcome patients in whom imipenem again seemed to perform better than the combined regimens.

Only one adverse effect was seen in our study, a surprising finding in view of the previous 10% to 20% incidence reported by others.[14,18,23] We attribute this to the inclusion in our study of only those side-effects which appeared related to the antibiotic regimen. Most notable was the unexpected absence of nephrotoxicity in the aminoglycoside-treated group. Solomkin and colleagues[14] reported a 20% incidence of nephrotoxicity with gentamicin use and stressed the difficulty in avoiding this condition in spite of serum level measurements and multiple dose adjustments. The data from our study do not support their findings and confirm the view that careful maintenance of aminoglycoside blood levels within the therapeutic range in conjunction with the use of the less nephrotoxic drug tobramycin can effectively prevent renal damage.

In conclusion, we have presented here data in support of the use of imipenem/cilastatin in intra-abdominal infection. Imipenem compares favourably to aminoglycoside-based regimens; it appears more effective and is not particularly toxic. Seriously ill patients are the ones most likely to benefit from this drug, as long as superinfections with resistant strains are carefully recognized and treated.

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Small-Bowel Lipoma: an Uncommon Cause of Obstruction

Wojciech Brzezinski, MD;* R.J. Bailey, MD, FRCPC;† Morris Besney, MD, FRCPC;‡ Garth Turner, MD, FRCPC§

Small-bowel tumours are an uncommon cause of small-bowel obstruction. The symptoms are unsually nonspecific and intermittent. Contrast studies of the small bowel are the best means of delineating the lesion. The authors present a case in which obstruction was treated with small-bowel resection, and they give a brief account of the occurrence of small-bowel tumours in a major teaching hospital.

Les tumeurs de l'intestin grêle sont rarement la cause d'obstruction. Les symptômes sont habituellement non spécifiques et intermittents. Des examens du grêle à l'aide de techniques de contraste sont le meilleur moyen de délinéer la tumeur. Les auteurs décrivent un cas où une obstruction fut traitée par résection et ils donnent un bref aperçu de l'incidence des tumeurs de l'intestin grêle dans un hôpital universitaire important.

Tumours of the small bowel are rare. They make up 1.5% to 6.5% of all gastrointestinal neoplasms.[1] Of these, 50% to 75% are malignant, accounting for 1% to 3% of all gastrointestinal malignant disease.[2] Benign tumours are often found at laparotomy performed for an unrelated condition. If they become symptomatic, the usual presentation involves bleeding, abdominal pain, nausea and vomiting.[3]

We describe a patient with a lipoma of the ileum who presented with intermittent obstruction of the small bowel.

Case Report

An 82-year-old woman was admitted with a 3-day history of intermittent upper abdominal pain, nausea and vomiting aggravated by eating. She had had similar symptoms over the last 2 or 3 years. About 30 years earlier she had undergone cholecystectomy.

She was found to have mild abdominal distension, with tenderness of the upper abdomen. No masses or blood was apparent on rectal examination. An x-ray film of the abdomen showed a number of air–fluid levels in the small bowel (Fig. 1). All symptoms resolved rapidly with conservative management. An upper-gastrointestinal-tract series with small-bowel follow-through showed a large intraluminal lesion in the ileum (Fig. 2).

At a subsequent laparotomy the segment of ileum containing the tumour (Fig. 3) was resected. Histopathologic examination of the lesion demonstrated that it was a

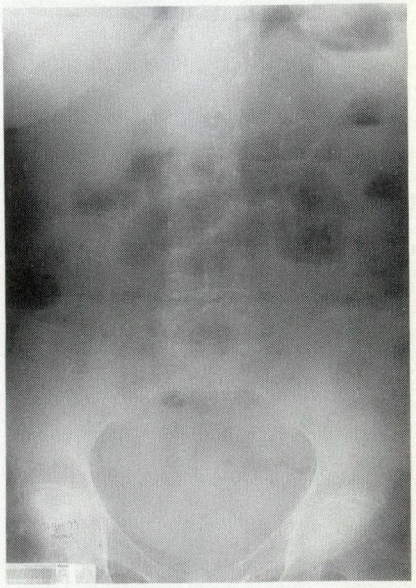

FIG. 1. X-ray film of abdomen, patient upright, shows air-fluid levels in several loops of abnormally distended small bowel.

From the University of Alberta and Royal Alexandra Hospital, Edmonton, Alta.

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benign lipoma. The patient's postoperative course was uncomplicated.

Discussion

Small-bowel lipomas account for 20% to 25% of all gastrointestinal lipomas, being second in frequency to those of the colon, which constitute 65% to 75% of cases.[4,5] Lipomas also account for 8% to 20% of all benign neoplasms of the small bowel, the most common being leiomyomas and adenomatous polyps.

Lipomas are usually single, submucosal masses. In 10% to 15% of cases they are multiple. A few rare cases of diffuse lipomatosis have been described.[6,7] Malignant transformation has not been reported. Fewer than half of the patients who have intestinal lipoma become symptomatic because of obstruction, intussusception or bleeding.[8]

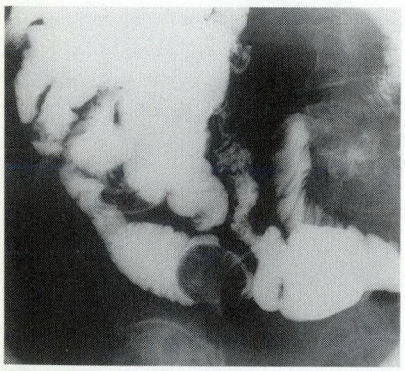

FIG. 2. Spot film from small-bowel follow-through shows smooth, nonpedunculated lesion, 4 cm in diameter, in ileum.

The diagnosis of small-bowel tumours is not always easy. A small-bowel follow-through may reveal (as it did in our case) the presence of a smooth, rounded filling defect. Fluoroscopy may offer additional help, showing mobility if the tumour is pedunculated and identifying normal bowel-wall motility. Excision of the benign tumour can be accomplished by enterotomy or a segmental resection. Surgical resection of a malignant lesion would have to be more extensive.

Reviewing the records of the Royal Alexandra Hospital in Edmonton we found that 46 patients with small-bowel tumours had been operated on between 1970 and 1988. In 19 patients the tumour was benign and in 27 it was malignant. The most common benign tumour in this group was leiomyoma (six cases). Among malignant lesions, we found adenocarcinomas in 18 cases, carcinoids in 6, sarcomas in 2 and lymphoma in 1 case.

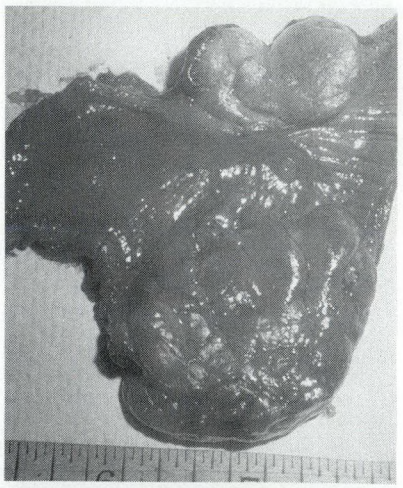

FIG. 3. Gross appearance of lipoma removed from small bowel.

We thank the staff of the Medical Records Department, Royal Alexandra Hospital for assistance in preparing data and Miss Brandingen for preparing the manuscript.

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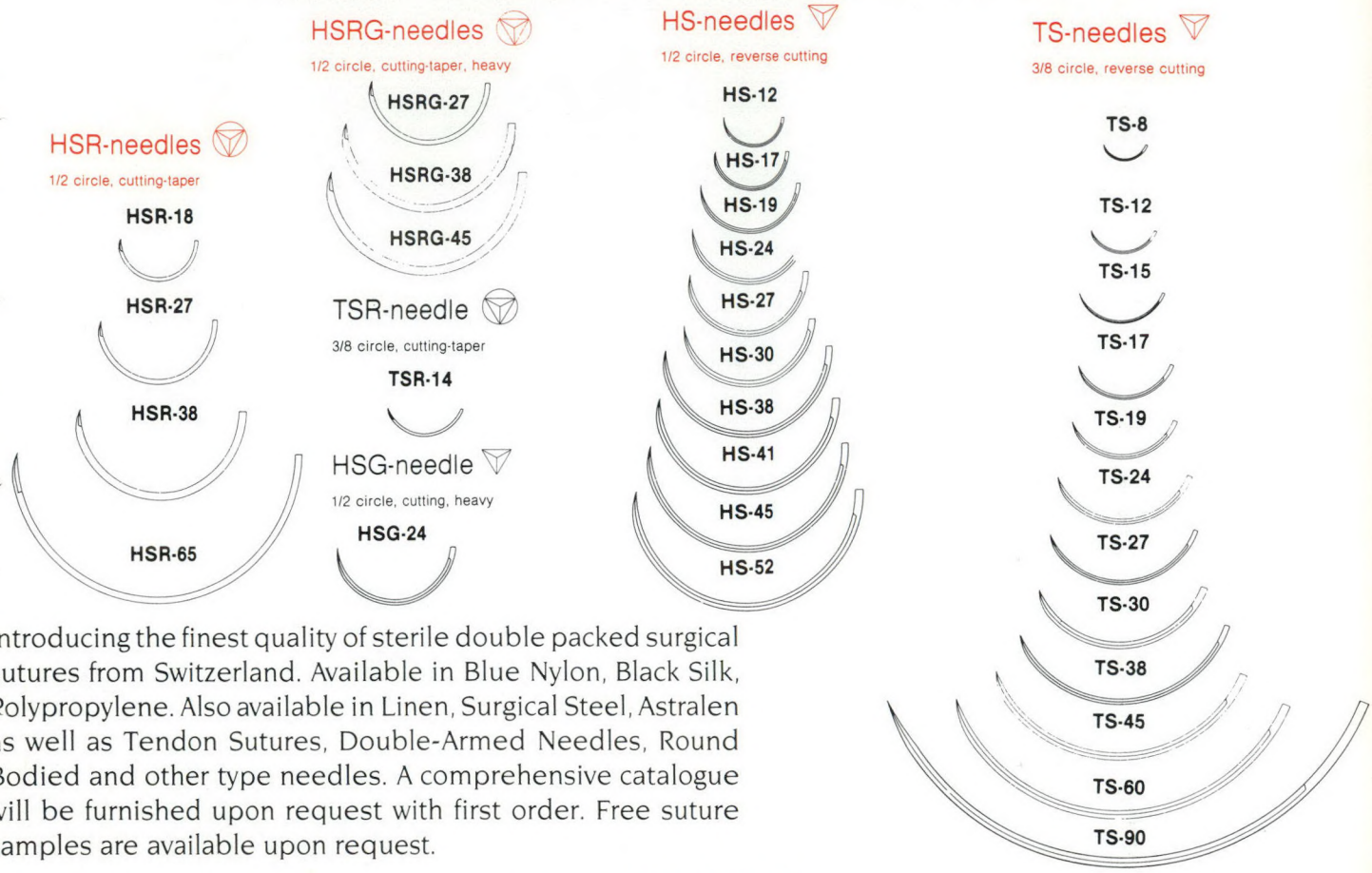

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